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Summary of the invention

This invention relates to peptides which are fragments of protein products arising from frameshift mutations in genes, which peptides elicit T cellular immunity, and to cancer vaccines and compositions for anticancer treatment comprising said peptides.

The invention further relates to a method for identifying such peptides which are fragments of protein products arising from frameshift mutations in genes, which may elicit T cellular immunity which is useful for combating cancer associated with said mutated genes.

The invention also relates to DNA sequences encoding at least one frameshift mutant peptide, and vectors comprising at least one insertion site containing a DNA sequence encoding at least one frameshift mutant peptide.

Further the invention relates to methods for the treatment or prophylaxis of cancers associated with frameshift mutations in genes by administration of at least one frameshift mutant peptide or a recombinant virus vector comprising at least one insertion site containing a DNA sequence encoding at least one frameshift mutant peptide, or an isolated DNA sequence comprising a DNA sequence encoding at least one frameshift mutant peptide.

The present invention represents a further development of anticancer treatment or prophylaxis based on the use of peptides to generate activation and strengthening of the

anti cancer activity of the T cellular arm of the body's own immune system.

Technical Background

Tumour antigens, Status:

T cell defined antigens have now been characterised in a broad spectrum of cancer types. These antigens can be divided into several main groups, depending on their expression. The two main groups are constituted by developmental differentiation related antigens (tumour-testis antigens, oncofoetal antigens etc., such as MAGE antigens and CEA) and tissue specific differentiation antigens (Tyrosinase, gp100 etc.). The group containing the truly tumour specific antigens contains proteins that are altered due to mutations in the genes encoding them. In the majority of these, the mutations are unique and have been detected in a single or in a small number of tumours. Several of these antigens seem to play a role in oncogenesis.

Cancer vaccines, Status:

The focus in cancer vaccine development has been on antigens expressed in a high degree within one form of cancer (such as melanoma) or in many kinds of cancers. One reason for this is the increased recruitment of patients into clinical protocols. The field is in rapid growth, illustrated by the accompanying table listing the cancer vaccine protocols currently registered in the PDQ database of NCI.

Inheritable cancer/cancer gene testing:

Inherited forms of cancer occur at a certain frequency in the population. For several of these cancer forms, the underlying genetic defects have been mapped. This is also the case in Lynch syndrome cancers which constitute an important group of inheritable cancer. In families inflicted with this syndrome, family members inherit defect genes encoding DNA Mismatch Repair (MMR) Enzymes. Carriers of such MMR defects frequently develop colorectal cancer (HNPCC) and other forms of cancer (list?). Mutations in MMR enzymes can be detected using gene testing in the same way as other cancer related genes can be detected.

Gene testing of risk groups in this case represents an ethical dilemma, since no acceptable forms for prophylactic treatment exist. At present surgery to remove the organ in danger to develop cancer has been the only treatment option. In these patients, cancer vaccines will be a very (interesting) form of prophylaxis, provided efficient vaccines can be developed.

The lack of efficient repair of mismatched DNA results in deletions and insertions in one strand of DNA, and this happens preferentially in stretches of DNA containing repeated units (repeat sequences). Until now, focus has been on repeat sequences in the form of non-coding microsattelite loci. Indeed microsattelite instability is the hallmark of cancers resulting from MMR defects. We have taken another approach, and have concentrated on frameshift mutations occurring in DNA sequences coding for proteins related to the oncogenic process. Such frameshift mutations result in completely new amino acid sequences in the C-terminal part of the proteins, prematurely terminating where a novel stop codon appears. This results in two important consequences:

1) The truncated protein resulting from the frameshift is generally nonfunctional, in most cases resulting in "knocking out" of an important cellular function. Aberrant proteins may also gain new functions such as the capacity to aggragate and form plaques. In both cases the frameshift results in disease.

2) The short new C-terminal amino acid sequence resulting from the shift in the reading frame (the "frameshift sequence") is foreign to the body. It does not exist prior to the mutation, and it only exists in cells having the mutation, i.e. in tumour cells and their pre malignant progenitors. Since they are completely novel and therefore foreign to the immune system of the carrier, they may be recognised by T-cells in the repertoire of the carrier. So far, nobody has focused on this aspect of frameshift mutations, and no reports exist on the characterisation of frameshift peptides from coding regions of proteins as tumour antigens. This concept is therefore novel and forms the basis for developing vaccines based on these sequences. It follows that such vaccines may also be used prophyllactively in persons who inherit defective enzymes belonging to the MMR machinery. Such vaccines will therefore fill an empty space in the therapeutic armament against inherited forms of cancer.

It has been shown that single amino acid substitutions in intracellular "self"-proteins may give rise to tumour rejection antigens, consisting of peptides differing in their amino acid sequence from the normal peptide. The T cells which recognise these peptides in the context of the major histocompatibility (MHC) molecules on the surface of the tumour cells, are capable of killing the tumour cells and thus rejecting the tumour from the host.

In contrast to antibodies produced by the B cells, which typically recognise a free antigen in its native conformation and further potentially recognise almost any site exposed on the antigen surface, T cells recognise an antigen only if the antigen is bound and presented by a MHC molecule. Usually this binding will take place only after appropriate antigen processing, which comprises a proteolytic fragmentation of the protein, so that the resulting peptide fragment fits into the groove of the MHC molecule. Thereby T cells are enabled to also recognise peptides derived from intracellular proteins. T cells can thus recognise aberrant peptides derived from anywhere in the tumour cell, in the context of MHC molecules on the surface of the tumour cell, and can subsequently be activated to eliminate the tumour cell harbouring the aberrant peptide.

M.Barinaga, Science, 257, 880-881, 1992 offers a short review of how MHC binds peptides. A more comprehensive explanation of the Technical Background for this Invention may be found in D. Male et al, Advanced Immunology, 1987, J.B.lippincott Company, Philadelphia. Both references are hereby included in their entirety.

The MHC molecules in humans are normally referred to as HLA (human leukocyte antigen) molecules. They are encoded by the HLA region on the human chromosome No 6.

The HLA molecules appear as two distinct classes depending on which region of the chromosome they are encoded by and which T cell subpopulations they interact with and thereby activate primarily. The class I molecules are encoded by the HLA A, B and C subloci and they primarily activate CD8+ cytotoxic T cells. The HLA class II molecules are encoded by the DR, DP and DQ

subloci and primarily activate CD4+ T cells, both helper cells and cytotoxic cells.

Normally every individual has six HLA Class I molecules, usually two from each of the three groups A, B and C. Correspondingly, all individuals have their own selection of HLA Class II molecules, again two from each of the three groups DP, DQ and DR. Each of the groups A, B, C and DP, DQ and DR are again divided into several subgroups. In some cases the number of different HLA Class I or II molecules is reduced due to the overlap of two HLA subgroups.

All the gene products are highly polymorphic. Different individuals thus express distinct HLA molecules that differ from those of other individuals. This is the basis for the difficulties in finding HLA matched organ donors in transplantations. The significance of the genetic variation of the HLA molecules in immunobiology is reflected by their role as immune-response genes. Through their peptide binding capacity, the presence or absence of certain HLA molecules governs the capacity of an individual to respond to peptide epitopes. As a consequence, HLA molecules determine resistance or susceptibility to disease.

T cells may control the development and growth of cancer by a variety of mechanisms. Cytotoxic T cells, both HLA class I restricted CD8+ and HLA Class II restricted CD4+, may directly kill tumour cells carrying the appropriate tumour antigens. CD4+ helper T cells are needed for cytotoxic CD8+ T cell responses as well as for antibody responses, and for inducing macrophage and LAK cell killing.

A requirement for both HLA class I and II binding is that the peptides must contain a binding motif, which usually

is different for different HLA groups and subgroups. A binding motif is characterised by the requirement for amino acids of a certain type, for instance the ones carrying large and hydrophobic or positively charged side groups, in definite positions of the peptide so that a narrow fit with the pockets of the HLA binding groove is achieved. The result of this, taken together with the peptide length restriction of 8-10 amino acids within the binding groove, is that it is quite unlikely that a peptide binding to one type of HLA class I molecules will also bind to another type. Thus, for example, it may very well be that the peptide binding motif for the HLA-A1 and HLA-A2 subgroups, which both belong to the class I gender, are as different as the motifs for the HLA-A1 and HLA-B1 molecules.

For the same reasons it is not likely that exactly the same sequence of amino acids will be located in the binding groove of the different class II molecules. In the case of HLA class II molecules the binding sequences of peptides may be longer, and it has been found that they usually contain from 10 to 16 amino acids, some of which, at one or both terminals, are not a part of the binding motif for the HLA groove.

However, an overlap of the different peptide binding motifs of several HLA class I and class II molecules may occur. Peptides that have an overlap in the binding sequences for at least two different HLA molecules are said to contain "nested T cell epitopes". The various epitopes contained in a "nested epitope peptide" may be formed by processing of the peptide by antigen presenting cells and thereafter be presented to T cells bound to different HLA molecules. The individual variety of HLA molecules in humans makes peptides containing nested epitopes more useful as general vaccines than peptides

that are only capable of binding to one type of HLA molecule.

Effective vaccination of an individual can only be achieved if at least one type of HLA class I and/or II molecule in the patient can bind a vaccine peptide either in it's full length or as processed and trimmed by the patient's own antigen presenting cells.

The usefulness of a peptide as a general vaccine for the majority of the population increases with the number of different HLA molecules it can bind to, either in its full length or after processing by antigen presenting cells.

In order to use peptides derived from a protein encoded by a mutated gene as vaccines or anticancer agents to generate anti tumour CD4+ and/or CD8+ T cells, it is necessary to investigate the mutant protein in question and identify peptides that are capable, eventually after processing to shorter peptides by the antigene presenting cells, to stimulate T cells.

Prior art

In our International Application PCT/NO92/00032 (published as WO92/14756), we described synthetic peptides and fragments of oncogene protein products which have a point of mutation or translocations as compared to their proto-oncogene or tumour suppressor gene protein. These peptides correspond to, completely cover or are fragments of the processed oncogene protein fragment or tumour suppressor gene fragment as presented by cancer cells or other antigen presenting cells, and are presented as a HLA-peptide complex by at least one allele in every individual. These peptides were also shown to

induce specific T cell responses to the actual oncogene protein fragment produced by the cell by processing and presented in the HLA molecule. In particular, we described peptides derived from the p21 *ras* protein which had point mutations at particular amino acid positions, namely position 12, 13 and 61. These peptides have been shown to be effective in regulating the growth of cancer cells *in vitro*. Furthermore, the peptides were shown to elicit CD4+ T cell immunity against cancer cells harbouring the mutated p21 *ras* oncogene protein through the administration of such peptides in vaccination or cancer therapy schemes. Later we have shown that these peptides also elicit CD8+ T cell immunity against cancer cells harbouring the mutated p21 *ras* oncogene protein through the administration mentioned above. * reflect Hg doc 2a

However, the peptides described above will be useful only in certain number of cancers, namely those which involve oncogenes with point mutations or translocation in a proto-oncogene or tumour suppressor gene. There is therefore a strong need for an anticancer treatment or vaccine which will be effective against a more general range of cancers.

In general, tumors are very heterogenous with respect to genetic alterations found in the tumour cells. This implies that both the potential therapeutic effect and prophylactic strength of a cancer vaccine will increase with the number of targets that the vaccine is able to elicit T cell immunity against. A multiple target vaccine will also reduce the risk of new tumour formation by treatment escape variants from the primary tumour.

Definition of Problem solved by the Invention.

There is a continuing need for new anticancer agents based on antigenic peptides giving rise to specific T cellular responses and toxicity against tumours and cancer cells carrying genes with mutations related to cancer. The present invention will contribute largely to supply new peptides that can have a use in the combat and prevention of cancer as ingredients in a multiple target anti-cancer vaccine.

Another problem solved by the present invention is that a protection or treatment can be offered to the individuals belonging to family's or groups with high risk for hereditary cancers. Hereditary cancers are in many cases associated with genes susceptible to frameshift mutations as described in this invention (i.e. mutations in mismatch repair genes). Today it is possible to diagnose risk of getting hereditary cancer but no pharmaceutical method for protection against the onset of the cancer is available.

Definition of the Invention

A main object of the invention is to obtain peptides corresponding to peptide fragments of mutant proteins produced by cancer cells which can be used to stimulate T cells.

Another main object of the invention is to develop a cancer therapy for cancers based on the T cell immunity which may be induced in patients by stimulating their T cells either *in vivo* or *in vitro* with the peptides according to the invention.

A third main object of the invention is to develop a vaccine to prevent the establishment of or to eradicate cancers based solely or partly on peptides corresponding to peptides of the present invention which can be used to generate and activate T cells which produce cytotoxic T cell immunity against cells harbouring the mutated genes.

A fourth main object of the invention is to design an anticancer treatment or prophylaxis specifically adapted to a human individual in need of such treatment or prophylaxis, which comprises administering at least one peptide according to this invention.

These and other objects of the invention are achieved by the attached claims.

Since frameshift mutations result in premature stop codons and therefore deletion in large parts of the proteins, proteins with frameshift mutations have generally not been considered to be immunogenetic and have therefore not been considered as targets for immunotherapy. Thus it has now surprisingly been found that a whole group of new peptides resulting from frameshift mutations in tumour relevant genes are useful for eliciting T cell responses against cancer cells harbouring genes with such frameshift mutations.

Genes containing a mono nucleoside base repeat sequence of at least five residues, for example of eighth deoxyadenosine bases (AAAAAAAA), or a di-nucleoside base repeat sequence of at least ~~four~~ two* di-nucleoside base units, for example of two deoxyadenosine-deoxycytosine units (ACAC), are susceptible to frameshift mutations. The frameshift mutations occur, respectively, either by insertion of one or two of the mono-nucleoside base residue or of one or two of the di-nucleoside base unit

* se dok 2a

in the repeat sequence, or by deletion of one or two of the mono-nucleoside base residue or of one or two of the di-nucleoside base unit from the repeat sequence. A gene with a frameshift mutation will from the point of mutation code for a protein with a new and totally different amino acid sequence as compared to the normal gene product. This mutant protein with the new amino acid sequence at the carboxy end will be specific for all cells carrying the modified gene.

In the remainder of this specification and claims the denomination frameshift mutant peptides will comprise such proteins and peptide fragments thereof.

It has now according to the present invention been found that such new protein sequences arising from frameshift mutations in genes in cancer cells give rise to tumour rejection antigens that are recognised by T cells in the context of HLA molecules.

It has further according to the present invention been found a group of peptides corresponding to fragments of mutant proteins arising from frameshift mutations in genes in cancer cells which can be used to generate T cells. The said peptides can therefore also be used to rise a T cell activation against cancer cells harbouring a gene with a frameshift mutation as described above.

These peptides are at least 8 amino acids long and correspond, either in their full length or after processing by antigen presenting cells, to the mutant gene products or fragments thereof produced by cancer cells in a human patient afflicted with cancer.

A peptide according to this invention is characterised in that it

a) is at least 8 amino acids long and is a fragment of a mutant protein arising from a frameshift mutation in a gene of a cancer cell;

and

b) consists of at least one amino acid of the mutant part of a protein sequence encoded by said gene;

and

c) comprises 0-10 amino acids from the carboxyl terminus of the normal part of the protein sequence preceding the amino terminus of the mutant sequence and may further extend to the carboxyl terminus of the mutant part of the protein as determined by a new stop codon generated by the frameshift mutation in the gene;

and

d) induces, either in its full length or after processing by antigen presenting cell, T cell responses.

The peptides of this invention contain preferably 8-25, 9-20, 9-16, 8-12 or 20-25 amino acids. They may for instance contain 9, 12, 13, 16 or 21 amino acids.

It is most preferred that the peptides of the present invention are at least 9 amino acids long, for instance 9-18 amino acids long, but due to the processing

possibility of the antigen presenting cells also longer peptides are very suitable for the present invention. Thus the whole mutant amino acid sequence may be used as a frameshift mutant peptide according to the present invention, if it comprises 8 amino acids or more.

The invention further relates to a method for vaccination of a person disposed for cancer, associated with a frameshift mutation in a gene, consisting of administering at least one peptide of the invention one or more times in an amount sufficient for induction of T-cell immunity to the mutant proteins encoded by the frameshift mutated gene.

The invention also relates to a method for treatment of a patient afflicted with cancer associated with frameshift mutation in genes, consisting of administering at least one peptide of the invention one or more times in an amount sufficient for induction of T-cell immunity to mutant proteins arising from frameshift mutations in the genes of cancer cells.

Furthermore, it has according to the present invention been found a method for identifying new peptides which correspond to fragments of proteins arising from frameshift mutations in genes. This method is characterised by the following steps:

1) identifying a gene in a cancer cell susceptible to frameshift mutation by having a mono nucleoside base repeat sequence of at least five residues, or a di-nucleoside base repeat sequence of at least four di-nucleoside base units;

and

2) removing, respectively, one nucleoside base residue or one di-nucleoside base unit from the repeat sequence and identifying the amino acid sequence of the protein encoded by the altered gene sequence as far as to include a new stop codon;

and/or

3) removing, respectively, two nucleoside base residues or two di-nucleoside base units from the repeat sequence and identifying the amino acid sequence of the protein encoded by the altered gene sequence as far as to include a new stop codon;

and/or

4) inserting, respectively, one nucleoside base residue or one di-nucleoside base unit in the repeat sequence and identifying the amino acid sequence of the protein encoded by the altered gene sequence as far as to include a new stop codon;

and/or

5) inserting, respectively, two nucleoside base residues or two di-nucleoside base units in the repeat sequence and identifying the amino acid sequence of the protein encoded by the altered gene sequence as far as to include a new stop codon.

In order to determine whether the peptides thus identified are useable in the compositions and methods according to the present invention for the treatment or prophylaxis of cancer, the following further step should be performed:

6) determining whether the new peptide, either in their full length or as shorter fragments of the peptides, are able to stimulate T cells.

Optionally a further step may be added as follows:

7) determining peptides containing nested epitopes for different major HLA class I and/or HLA class II molecules.

Detailed Description of the invention.

In the present description and claims, the amino acids are represented by their one letter abbreviation as known in the art.

The peptides of the present invention shall be explicitly exemplified through two different embodiments, wherein cancer develops based on frameshift mutations in specific genes, namely the BAX gene and TGFβRII gene:

I) BAX gene
It has been established that the BAX gene is involved in regulation of survival or death of cells by promoting apoptosis. The human BAX gene contains a repeat sequence of eight deoxyguanosine bases (G8) in the third exon, spanning codons 38 to 41 (ATG GGG GGG GAG).

Frameshift mutations in this G8 repeat have been observed, both as G7 (ATG GGG GGG AGG) and G9 (ATG GGG GGG GGA) repeats, both in colon cancer cells and prostate cancer cells. The occurency is more than 50% of the examined cases (Rampino, N. et al., "Somatic frameshift

mutations in the BAX gene in colon cancers of the microsatellite mutator phenotype.", Science (Washington DC), 275: 967-969, 1997). The modified BAX gene products are unable to promote apoptosis and thus makes further tumour progress possible. Furthermore the modified gene products are only found in cancer cells and are therefore targets for specific immunotherapy.

According to the present invention, peptides corresponding to the transformed BAX protein products arising from frameshift mutations in the BAX gene can be used as anticancer therapeutical agents or vaccines with the function to trigger the cellular arm of the immune system (T-cells) against cancer cells in patients afflicted with cancers associated with a modified BAX gene.

Frameshift mutations in the BAX gene result in mutant peptide sequences with the first amino acid of the altered sequence in position 41 as compared to the normal BAX protein (Table 1, seq.id. no. 1 to 4).

Table 1

amino acid pos	41	51	61	71
normal bax peptide ;	EAPELALDPV	PQDASTKKLS	ECLKRIGDEL	DS...
seq id no 1(bax-1G);	RHPSWPWTRC	LRMRPPRS		
seq id no 4(bax+2G);	GRHPSWPWTR	CLRMRPPRS		
seq id no 2(bax-2G);	GTRAGPGPGA	SGCVHQEAER	VSQAHRGRTG	Q
seq id no 3(bax+1G);	GGTRAGPGPG	ASGCVHQEAE	RVSQAHRGRT	GQ

Table 2 shows one group of peptides according to the present invention:

Table 2

seq.id.no. 5: IQDRAGRMGGRHPSWPWTRCLRMRPPRS

seq.id.no. 6: IQDRAGRMGGGRHPSWPWT
seq.id.no. 7: IQDRAGRMGGGGTRAGPGPGASGCVHQEAERVSQAHRGRTGQ
seq.id.no. 8: IQDRAGRMGGGTRAGPGPG

The peptides listed in Table 3 were used for *in vitro* generation of T cells that recognise mutant BAX peptides.

Table 3.

seq id no 1: RHPSWPWTRCLRMRPPRS
seq id no 9: IQDRAGRMGGRHPSWPWTRCLR
seq id no 6: IQDRAGRMGGGRHPSWPWT
seq id no 10: ASGCVHQEAERVSQAHRGRTGQ
seq id no 11: GGTRAGPGPGASGCVHQEAERV
seq id no 12: IQDRAGRMGGGGTRAGPGPGAS
seq id no 8: IQDRAGRMGGGTRAGPGPG

The most preferred peptides according to this embodiment of the present invention are listed in Table 4:

Table 4

seq id no 1: RHPSWPWTRCLRMRPPRS
seq id no 2: GTRAGPGPGASGCVHQEAERVSQAHRGRTGQ
seq id no 3: GGTRAGPGPGASGCVHQEAERVSQAHRGRTGQ
seq id no 4: GRHPSWPWTRCLRMRPPRS
seq.id.no. 5: IQDRAGRMGGRHPSWPWTRCLRMRPPRS
seq.id.no. 6: IQDRAGRMGGGRHPSWPWT
seq.id.no. 7: IQDRAGRMGGGGTRAGPGPGASGCVHQEAERVSQAHRGRTGQ
seq id no 8: IQDRAGRMGGGTRAGPGPG
seq id no 9: IQDRAGRMGGRHPSWPWTRCLR
seq id no 10: ASGCVHQEAERVSQAHRGRTGQ
seq id no 11: GGTRAGPGPGASGCVHQEAERV
seq id no 12: IQDRAGRMGGGGTRAGPGPGAS

2) TGFβRII

It has been established that the TGFβRII gene is involved in regulation of cell growth. TGFβRII is a receptor for
It has recently also been shown ... se doc 2a

TGFβ which down regulates cell growth. The human gene coding for TGFβRII contains a repeat sequence of ten deoxyadenosine bases (A10) from base no. 709 to base no. 718 (GAA AAA AAA AAG CCT). In colon cancers and pancreatic cancers frameshift mutations in this A10 repeat have been observed, both as A9 (GAA AAA AAA AGC CT) and A11 (GAA AAA AAA AAA GCC) repeats, in approximately 80 % of the examined cases (Yamamoto, H., "Somatic frameshift mutations in DNA mismatch repair and proapoptosis genes in hereditary nonpolyposis colorectal cancer.", Cancer Research 58, 997-1003, March 1, 1998). The modified TGFβRII gene products are unable to bind TGFβ and the signal for down regulation of cell growth is eliminated and thus makes further tumour progress possible. Furthermore the modified gene products are only found in cancer cells and are therefore targets for immunotherapy.

Consequently peptides corresponding to the transformed TGFβRII protein products arising from frameshift mutations in the TGFβRII gene can be used as anticancer therapeutical agents or vaccines with the function to trigger the cellular arm of the immune system (T-cells) against cancer cells in patients afflicted with cancers associated with a modified TGFβRII gene.

Frameshift mutations in the TGFβRII gene result in mutant peptide sequences with the first amino acid of the altered sequence in either position 133 (one and two base deletions) or 134 (one and two base insertions) as compared to the normal TGFβRII protein (Table 5, seq id no 13 and 21).

Table 5.

amino acid pos. 133

normal TGFβRII ; K PGETFFMCSC SSDECNDNII FSEEYNTSNP DLLL

seq id no 13(-1A); S LVRLSSCVPV ALMSAMTTSS SQKNITPAIL TCC

seq id no 13(+2A); SLVRLSSCVP VALMSAMTTS SSQKNITPAI LTCC

TGFbRII + 1A) ; AW

TGFbRII - 2A) ; A W

Table 6 shows one groups of peptides of this invention:

Table 6

seq id no 14:SPKCIMKEKKSLVRLSSCVPVALMSAMTTSSSQKNITPAILTCC

seq id no 15:PKCIMKEKKKSLVRLSSCV

seq id no 19:SPKCIMKEKKAW

seq id no 20:PKCIMKEKKKAW

Table 7 presents peptides that were used for *in vitro* generation of T cells that recognise mutant TGFβRII peptides.

Table 7

seq id no 15: PKCIMKEKKKSLVRLSSCV

seq id no 16: ALMSAMTTSSSQKNITPAILTCC

seq id no 17: SLVRLSSCVPVALMSAMTTSSSQ

seq id no 18: SPKCIMKEKKSLVRLSSCVPVA

seq id no 19: SPKCIMKEKKAW

seq id no 20: PKCIMKEKKKAW

seq id no 21: AMTTSSSQKNITPAILTCC

seq id no 428: SLVRLSSCV

The most preferred peptides of this embodiment of the present invention are:

Table 8

seq id no 13:SLVRLSSCVPVALMSAMTTSSSQKNITPAILTCC

seq id no 14:SPKCIMKEKKSLVRLSSCVPVALMSAMTTSSSQKNITPAILTCC

seq id no 15:PKCIMKEKKKSLVRLSSCV

seq id no 16:ALMSAMTTSSSQKNITPAILTCC

seq id no 17:SLVRLSSCVPVALMSAMTTSSSQ

seq id no 18:SPKCIMKEKKSLVRLSSCVPVA

seq id no 19:SPKCIMKEKKAW

seq id no 20:PKCIMKEKKKAW

seq id no 21:AMTTSSSQKNITPAILTCC

seq id no428:SLVRLSSCV

Other peptides of the invention can be fragments of the peptides listed in the Tables 1-8 above. Such fragments are most preferred from 9-16 amino acids long and include at least one amino acid from the mutant part of the protein.

As used in this description and claims the term fragment is intended to specify a shorter part of a longer peptide or of a protein.

Other cancer associated genes containing repeat sequences of a nucleoside base and which therefore are susceptible to frameshift mutations and consequently are potential candidates for peptides according to the present invention (seq id nos according to table 9 are given in parentheses in each case) are the following:

Human TGF-β-2 (hTGFβ2) gene (seq id nos 22-29)

Deleted in colorectal cancer (DCC) gene (seq id nos 30-34)

Human breast and ovarian cancer susceptibility (BRCA1) gene (seq id nos 378-387)

Human breast cancer susceptibility (BRCA2) gene (seq id nos 35-94)
Human protein tyrosine phosphatase (hPTP) gene (seq id nos 95-102)
Human DNA topoisomerase II (top2) gene (seq id nos 103-108)
Human kinase (TTK) gene (seq id nos 109-120)
Human transcriptional repressor (CTCF) gene (seq id nos 121-127)
Human FADD-homologous ICE/CED-3-like protease gene (seq id nos 128-133)
Human putative mismatch repair/binding protein (hMSH3) gene (seq id nos 134-147)
Human retinoblastoma binding protein 1 isoform I (hRBP1) gene (seq id nos 148-156)
Human FMR1 (hFMR1) gene (seq id nos 157-161)
Human TINUR gene (seq id nos 162-169)
b-raf oncogene (seq id nos 170-175)
Human neurofibromin (NF1) gene (seq id nos 176-181)
Human germline n-myc gene (seq id nos 182-188)
Human n-myc gene (seq id nos 189-194)
Human ras inhibitor gene (seq id nos 195-199)
Human hMSH6 gene (seq id nos 200-203 and 293-297)
Human nasopharynx carcinoma EBV BNLF-1 gene (seq id nos 204-210)
Human cell cycle regulatory protein (E1A-binding protein) p300 gene (seq id nos 211-218)
Human B-cell lymphoma 3-encoded protein (bcl-3) gene (seq id nos 219-226)
Human transforming growth factor-beta induced gene product (BIGH3) (seq id nos 227-232)
Human transcription factor ETV1 gene (seq id nos 233-239)
Human insulin-like growth factor binding protein (IGFBP4) gene (seq id nos 240-246)
Human MUC1 gene (seq id nos 247-266)
Human protein-tyrosine kinase (JAK1) gene (seq id nos 267-271)

Human protein-tyrosine kinase (JAK3) gene (seq id nos 272-279)

Human Flt4 gene (for transmembrane tyrosinase kinase) (seq id nos 280-284)

Human p53 associated gene (seq id nos 285-292)

Human can (hCAN) gene (seq id nos 298-300)

Human DBL (hDBL) proto-oncogene / Human MCF2PO (hMCF2PO) gene (seq id nos 301-306)

Human dek (hDEK) gene (seq id nos 307-309)

Human retinoblastoma related protein (p107) gene (seq id nos 310-313)

Human G protein-coupled receptor (hGPR1) gene (seq id nos 314-319)

Human putative RNA binding protein (hRBP56) gene (seq id nos 320-325)

Human transcription factor (hITF-2) gene (seq id nos 326-327)

Human malignant melanoma metastasis-supressor (hKiSS-1) gene (seq id nos 328-334)

Human telomerase-associated protein TP-1 (hTP-1) gene (seq id nos 335-348)

Human FDF-5 (hFDF-5) gene (seq id nos 349-356)

Human metastasis-assosiated mta1 (hMTA1) gene (seq id nos 357-362)

Human transcription factor TFIIB 90 kDa subunit (hTFIIB90) gene (seq id nos 363-369)

Human tumour suppressor (hLUCA-1) gene (seq id nos 370-377)

Human Wilm's tumour (WIT-1) associated protein (seq id nos 388-393)

Human cysteine protease (ICErel-III) gene (seq id nos 394-398)

Human Fas ligand (FasL) gene (seq id nos 399-403)

Human BRCA1-associated RING domain protein (BARD1) gene (seq id nos 404-417)

Human mcf.2 (hMCF.2) gene (seq id nos 418-422)

Human Fas antigen (fas) gene (seq id nos 423-427)

Human DPC4 gene (seq id nos 429-437).

The mutant peptides that are the results of frameshift mutation in these genes, in accordance with the present invention, are listed in table 9.

Table 9

seq id no 22; TVGRPHISC
seq id no 23; KTVGRPHISC
seq id no 24; KQWEDPTSPANVIALLQT
seq id no 25; QWEDPTSPANVIALLQT
seq id no 26; QKTIKSTRKKTVGRPHISC
seq id no 27; QKTIKSTRKKKTVGRPHISC
seq id no 28; QKTIKSTRKKKQWEDPTSPANVIALLQT
seq id no 29; QKTIKSTRKKQWEDPTSPANVIALLQT
seq id no 30; AADLQQQFVHFLDCWDVSSIPFTLHLPQAQDITT
seq id no 31; GKDAKEKSS
seq id no 32; GKDAKEKKSS
seq id no 33; GKDAKEKKAADLQQQFVHFLDCWDVSSIPFTLHLPQAQDITT
seq id no 34; GKDAKEKAADLQQQFVHFLDCWDVSSIPFTLHLPQAQDITT
seq id no 35; FSMKQTLMNVKNLKTK
seq id no 36; KFSMKQTLMNVKNLKTK
seq id no 37; VRTSKTRKKFSMKQTLMNVKNLKTK
seq id no 38; VRTSKTRKKKFSMKQTLMNVKNLKTK
seq id no 39; VRTSKTRKKNFP
seq id no 40; VRTSKTRKNFP
seq id no 41; IKKKLLQFQK
seq id no 42; KIKKKLLQFQK
seq id no 43; KSRRNYFNFKNNCQSRL
seq id no 44; SRRNYFNFKNNCQSRL
seq id no 45; TNLRVIQKIKKKLLQFQK
seq id no 46; TNLRVIQKKIKKKLLQFQK
seq id no 47; TNLRVIQKKSRRNYFNFKNNCQSRL
seq id no 48; TNLRVIQKSRRNYFNFKNNCQSRL
seq id no 49; KIMIT
seq id no 50; NIDKIPEKIMIT
seq id no 51; NIDKIPEKKIMIT

seq id no 52; IINAN
seq id no 53; KIINAN
seq id no 54; NDKTVSEKIINAN
seq id no 55; NDKTVSEKKIINAN
seq id no 56; NGLEKEYLMVNQKE
seq id no 57; SQTSLLEAKNGLEKEYLMVNQKE
seq id no 58; SQTSLLEAKKNGLEKEYLMVNQKE
seq id no 59; SQTSLLEAKKMA
seq id no 60; SQTSLLEAKMA
seq id no 61; TLVFPK
seq id no 62; KTLVFPK
seq id no 63; LKNVEDQKTLVFPK
seq id no 64; LKNVEDQKKTLVFPK
seq id no 65; LKNVEDQKKH
seq id no 66; LKNVEDQKH
seq id no 67; KKIQLY
seq id no 68; KKKIQLY
seq id no 69; RKRFSYTEYLASIIRFIFSVNRRKEIQNLSSCNFKI
seq id no 70; LRIVSYSKKKKIQLY
seq id no 71; LRIVSYSKKKKKIQLY
seq id no 72; LRIVSYSKKRKRFSYTEYLASIIRFIFSVNRRKEIQNLS--SCNFKI
seq id no 73; LRIVSYSKRKRFSYTEYLASIIRFIFSVNRRKEIQNLS--SCNFKI
seq id no 74; QDLPLSSICQTIVTIYWQ
seq id no 75; KQDLPLSSICQTIVTIYWQ
seq id no 76; NRTCPFRLFVRRMLQFTGNKVLDRP
seq id no 77; GFVVSVVKKQDLPLSSICQTIVTIYWQ
seq id no 78; GFVVSVVKKKQDLPLSSICQTIVTIYWQ
seq id no 79; GFVVSVVKKNRTCPFRLFVRRMLQFTGNKVLDRP
seq id no 80; GFVVSVVKNRTCPFRLFVRRMLQFTGNKVLDRP
seq id no 81; YRKTKNQN
seq id no 82; KYRKTKNQN
seq id no 83; NTERPKIRTN
seq id no 84; DETFYKGKKYRKTKNQN
seq id no 85; DETFYKGKKKYRKTKNQN

seq id no 86; DETFYKGKKNTERPKIRTN
seq id no 87; DETFYKGKNTERPKIRTN
seq id no 88; LSINNYRFQMKFYFRFTSHGSPFTSANF
seq id no 89; KLSINNYRFQMKFYFRFTSHGSPFTSANF
seq id no 90; NSVSTTTGFR
seq id no 91; NIQLAATKKLSINNYRFQMKFYFRFTSHGSPFTSANF
seq id no 92; NIQLAATKKKLSINNYRFQMKFYFRFTSHGSPFTSANF
seq id no 93; NIQLAATKKNSVSTTTGFR
seq id no 94; NIQLAATKNSVSTTTGFR
seq id no 95; MEHVAPGRMSASPQSPTQ
seq id no 96; KMEHVAPGRMSASPQSPTQ
seq id no 97; KWSTWLQAECQHLHSPQRSDKPQQAGLDQQHHCFALDS-
-SPGPRPVFLQLLGLMGQGRHD
seq id no 98; WSTWLQAECQHLHSPQRSDKPQQAGLDQQHHCFALDS-
-SPGPRPVFLQLLGLMGQGRHD
seq id no 99; TFSVWAEKMEHVAPGRMSASPQSPTQ
seq id no 100; TFSVWAEKKMEHVAPGRMSASPQSPTQ
seq id no 101; TFSVWAEKKWSTWLQAECQHLHSPQRSDKPQQAGLDQ-
-QHHCFALDSSPGPRPVFLQLLGLMGQGRHD
seq id no 102; TFSVWAEKWSTWLQAECQHLHSPQRSDKPQQAGLDQ-
-QHHCFALDSSPGPRPVFLQLLGLMGQGRHD
seq id no 103; HKWLKFCLLRLVKESFHE
seq id no 104; KHKWLKFCLLRLVKESFHE
seq id no 105; KGGKAKGKKHKWLKFCLLRLVKESFHE
seq id no 106; KGGKAKGKKKHKWLKFCLLRLVKESFHE
seq id no 107; KGGKAKGKKNTNG
seq id no 108; KGGKAKGKNTNG
seq id no 109; VNNFFKKL
seq id no 110; KVNNFFKKL
seq id no 111; LSQGNVKKVNNFFKKL
seq id no 112; LSQGNVKKKVNNFFKKL
seq id no 113; GEKNDLQLFVMSDRRYKIYWTVILLNPCGNLHLKTTSL
seq id no 114; KGEKNDLQLFVMSDRRYKIYWTVILLNPCGNLHLKTTSL
seq id no 115; KGKKMICSYS
seq id no 116; GKKMICSYS
seq id no 117; SSKTFEKKGEKNDLQLFVMSDRRYKIYWTVILLNPCGN-
-LHLKTTSL

seq id no 118; SSKTFEKKKGEKNDLQLFVMSDRRYKIYWTVILLNPCGN--LHLKTTSL

seq id no 119; SSKTFEKKKGKKMICSYS

seq id no 120; SSKTFEKKGKKMICSYS

seq id no 121; QRKPKRANCVIQRRAKM

seq id no 122; KQRKPKRANCVIQRRAKM

seq id no 123; NKENQKEQTALLYRGGQRCRCVCLRF

seq id no 123; NKENQKEQTALLYRGGQRCRCVCLRF

seq id no 124; PDYQPPAKKQRKPKRANCVIQRRAKM

seq id no 125; PDYQPPAKKKQRKPKRANCVIQRRAKM

seq id no 126; PDYQPPAKKNKENQKEQTALLYRGGQRCRCVCLRF

seq id no 127; PDYQPPAKNKENQKEQTALLYRGGQRCRCVCLRF

seq id no 128; NLSSLLI

seq id no 129; TCLPF

seq id no 130; QPTFTLRKNLSSLLI

seq id no 131; QPTFTLRKKNLSSLLI

seq id no 132; QPTFTLRKKTCLPF

seq id no 133; QPTFTLRKTCLPF

seq id no 134; RATFLLSLWECSLPQARLCLIVSRTGLLVQS

seq id no 135; GQHFYWHCGSAACHRRGCV

seq id no 136; KENVRDKKRATFLLSLWECSLPQARLCLIVSRTGLLVQS

seq id no 137; KENVRDKKKRATFLLSLWECSLPQARLCLIVSRTGLLVQS

seq id no 138; KENVRDKKKGQHFYWHCGSAACHRRGCV

seq id no 139; KENVRDKKGQHFYWHCGSAACHRRGCV

seq id no 140; ITHTRWGITTWDSWSVRMKANWIQAQQNKSLILSPSFTK

seq id no 141; KITHTRWGITTWDSWSVRMKANWIQAQQNKSLILSPSFTK

seq id no 142; KLLTPGGELPHGILGQ

seq id no 143; LLTPGGELPHGILGQ

seq id no 144; PPVCELEKITHTRWGITTWDSWSVRMKANWIQAQQNKS--LILSPSFTK

seq id no 145; PPVCELEKKITHTRWGITTWDSWSVRMKANWIQAQQNKS--LILSPSFTK

seq id no 146; PPVCELEKKLLTPGGELPHGILGQ

seq id no 147; PPVCELEKLLTPGGELPHGILGQ

seq id no 148; SLKDELEKMKI

seq id no 149; SLKDELEKKMKI

seq id no 150; LGQSSPEKKNKN
seq id no 151; LGQSSPEKNKN
seq id no 152; RLRRINGRGSQIRSRNAFNRSEE
seq id no 153; EPKVKEEKKT
seq id no 154; EPKVKEEKKKT
seq id no 155; EPKVKEEKKRLRRINGRGSQIRSRNAFNRSEE
seq id no 156; EPKVKEEKRLRRINGRGSQIRSRNAFNRSEE
seq id no 157; TFRYKGKQHPFFST
seq id no 158; GPNAPEEKNH
seq id no 159; GPNAPEEKKNH
seq id no 160; GPNAPEEKKTFRYKGKQHPFFST
seq id no 161; GPNAPEEKTFRYKGKQHPFFST
seq id no 162; MQNTCV
seq id no 163; KMQNTCV
seq id no 164; KCKIRVFSK
seq id no 165; CKIRVFSK
seq id no 166; FFKRTVQKMQNTCV
seq id no 167; FFKRTVQKKMQNTCV
seq id no 168; FFKRTVQKKCKIRVFSK
seq id no 169; FFKRTVQKCKIRVFSK
seq id no 170; LPHYLAH
seq id no 171; CLITWLTN
seq id no 172; GSTTGLSATPLPHYLAH
seq id no 173; GSTTGLSATPPLPHYLAH
seq id no 174; GSTTGLSATPPCLITWLTN
seq id no 175; GSTTGLSATPCLITWLTN
seq id no 176; RFADKPRPN
seq id no 177; DLPTSPDQTRSGPVHVSVEP
seq id no 178; DSAAGCSGTPRFADKPRPN
seq id no 179; DSAAGCSGTPPRFADKPRPN
seq id no 180; DSAAGCSGTPPDLPTSPDQTRSGPVHVSVEP
seq id no 181; DSAAGCSGTPDLPTSPDQTRSGPVHVSVEP
seq id no 182; AHPETPAQNRLRIPCSRREVRSRACKPPGAQGSDER-
-RGKASPGRDCDVRTGRP
seq id no 183; PAHPETPAQNRLRIPCSRREVRSRACKPPGAQGSDER-
-RGKASPGRDCDVRTGRP

seq id no 184; RPTRRHPRRIASGSPAVGGR

seq id no 185; VAIRGHPRPPAHPETPAQNRLRIPCSRREVRSRACKP-
-PGAQGSDERRGKASPGRDCDVRTGRP

seq id no 186; VAIRGHPRPPPAHPETPAQNRLRIPCSRREVRSRACKP-
-PGAQGSDERRGKASPGRDCDVRTGRP

seq id no 187; VAIRGHPRPPRPTRRHPRRIASGSPAVGGR

seq id no 188; VAIRGHPRPRPTRRHPRRIASGSPAVGGR

seq id no 189; RGRTSGRSLSCCRRPRCRPAVASRSTAPSPRAGSR-
-RCCLRTSCGAARPRRTRSACGDWVASPPTRSS-
-SRTACGAASPPARSWSAP

seq id no 190; GGGHLEEV

seq id no 191; YFGGPDSTPRGRTSGRSLSCCRRPRCRPAVASR-
-STAPSPRAGSRRCCLRTSCGAARPRRTRSACGD-
-WVASPPTRSSSRTACGAASPPARSWSAP

seq id no 192; YFGGPDSTPPRGRTSGRSLSCCRRPRCRPAVASR-
-STAPSPRAGSRRCCLRTSCGAARPRRTRSACGDW-
-VASPPTRSSSRTACGAASPPARSWSAP

seq id no 193; YFGGPDSTPPGGGHLEEV

seq id no 194; YFGGPDSTPGGGHLEEV

seq id no 195; HRVADP

seq id no 196; LSQSSELDPPSSR

seq id no 197; LSQSSELDPPPSSR

seq id no 198; LSQSSELDPPHRVADP

seq id no 199; LSQSSELDPHRVADP

seq id no 200; VILLPEDTPPS

seq id no 201; VILLPEDTPPPS

seq id no 202; VILLPEDTPPLLRA

seq id no 203; VILLPELDPLLRA

seq id no 204; PSPLP

seq id no 205; PLLFHRPCSPSPALGATVLAVYRYE

seq id no 206; LLFHRPCSPSPALGATVLAVYRYE

seq id no 207; APRPPLGPPSPLP

seq id no 208; APRPPLGPPPSPLP

seq id no 209; APRPPLGPPPLLFHRPCSPSPALGATVLAVYRYE

seq id no 210; APRPPLGPPLLFHRPCSPSPALGATVLAVYRYE

seq id no 211; TQVLPQGCSLSLLHTTFPHRQVPHILDW

seq id no 212; PTQVLPQGCSLSLLHTTFPHRQVPHILDW

seq id no 213; PLQSFPKDAASAFSTPRFPTDKFPTSWTGSCPGQPHGT-
-RAFCQPGPEFNAFSAC

seq id no 214; LQSFPKDAASAFSTPRFPTDKFPTSWTGSCPGQPHGT-
-RAFCQPGPEFNAFSAC

seq id no 215; PSPRPQSQPPTQVLPQGCSLSLLHTTFPHRQVPHILDW

seq id no 216; PSPRPQSQPPPTQVLPQGCSLSLLHTTFPHRQVPHILDW

seq id no 217; PSPRPQSQPPPLQSFPKDAASAFSTPRFPTDKFPTS-
-WTGSCPGQPHGTRAFCQPGPEFNAFSAC

seq id no 218; PSPRPQSQPPLQSFPKDAASAFSTPRFPTDKFPTS-
-WTGSCPGQPHGTRAFCQPGPEFNAFSAC

seq id no 219; TAWPGRRRFTTPEPYCLCTPLGPWAPRFLW

seq id no 220; PTAWPGRRRFTTPEPYCLCTPLGPWAPRFLW

seq id no 221; PRPGPAGGALLPRSLTAFVPHSGHGLPVSSGEPAYTPIP-
-HDVPHGTPPFC

seq id no 222; RPGPAGGALLPRSLTAFVPHSGHGLPVSSGEPAYTPIPH-
-DVPHGTPPFC

seq id no 223; DLPAVPGPPTAWPGRRRFTTPEPYCLCTPLGPWAPRFLW

seq id no 224; DLPAVPGPPPTAWPGRRRFTTPEPYCLCTPLGPWAPRFLW

seq id no 225; DLPAVPGPPPRPGPAGGALLPRSLTAFVPHSGHGLPVSSG-
-EPAYTPIPHDVPHGTPPFC

seq id no 226; DLPAVPGPPRPGPAGGALLPRSLTAFVPHSGHGLPVSSG-
-EPAYTPIPHDVPHGTPPFC

seq id no 227; QWGLSWMS

seq id no 228; NGDCHGCPEGRQSL

seq id no 229; FTMDRVLTPQWGLSWMS

seq id no 230; FTMDRVLTPPQWGLSWMS

seq id no 231; FTMDRVLTPPNGDCHGCPEGRQSL

seq id no 232; FTMDRVLTPNGDCHGCPEGRQSL

seq id no 233; HHPARQCPHCIMHLQTQLIHRNLTGPSQLTSLHRS-
-PYQIAATPWTTDFAASFFLNPVTPFLLCRRCQGKDV-
-LCTNARCLSQTSPSHHKALSRTTTQCMNT-
-TPWLAVRPAKAFPLL

seq id no 234; PHHPARQCPHCIMHLQTQLIHRNLTGPSQLTSLHRS-
-PYQIAATPWTTDFAASFFLNPVTPFLLCRRCQGK-
-DVLCTNARCLSQTSPSHHKALSRTTTQCMNTTP-
-WLAVRPAKAFPLL

seq id no 235; HTIQHASVPTASCISKLNSYTEN

seq id no 236; PQVGMRPSNPPHHPARQCPHCIMHLQTQLIHRNLT-
-GPSQLTSLHRSPYQIAATPWTTDFAASFFLNPVTPFL-
-LCRRCQGKDVLCTNARCLSQTSPSHHKALSRTTTQC-
-MNTTPWLAVRPAKAFPLL

seq id no 237; PQVGMRPSNP PPHHPARQCPHCIMHLQTQLIHRNLTGPS-
-QLTSLHRSPYQIAATPWTTDFAASFFLNPVTPFLLCRRC-
-QGKDVLCTNARCLSQTSPSHHKALSRTTTQCMNTTPWLA-
-VRPAKAFPLL

seq id no 238; PQVGMRPSNPPHTIQHASVPTASCISKLNSYTEN

seq id no 239; PQVGMRPSNPHTIQHASVPTASCISKLNSYTEN

seq id no 240; WAARSWCERRAAAVAPLAPWAWGCPAGCTPPVAARAC-
-AATRPEGWRSPCTH

seq id no 241; PWAARSWCERRAAAVAPLAPWAWGCPAGCTPPVAA-
-RACAATRPEGWRSPCTH

seq id no 242; RGLRGAGARGGLRLLRHLRPGLGDALRGVHPPLR-
-LGPALLPAPRGGEAPAHTDARARRVHGAGGDRGHPGPAAL

seq id no 243; EEKLARCRPPWAARSWCERRAAAVAPLAPWAWGCPAGC-
-TPPVAARACAATRPEGWRSPCTH

seq id no 244; EEKLARCRPPPWAARSWCERRAAAVAPLAPWAWGCPA-
-GCTPPVAARACAATRPEGWRSPCTH

seq id no 245; EEKLARCRPPRGLRGAGARGGLRLLRHLRPGLGDA-
-LRGVHPPLRLGPALLPAPRGGEAPAHTDARARRVHGAGG-
-DRGHPGPAAL

seq id no 246; EEKLARCRPRGLRGAGARGGLRLLRHLRPGLGDALRG-
-VHPPLRLGPALLPAPRGGEAPAHTDARARRVHGAGG-
-DRGHPGPAAL

seq id no 247; QPPVSPRPRRPGRPRAPPPPQPMVSPRRRTTGPPW-
-RPPPLQSTMSPPPQALHQAQLLLWCTTAPLPGLPQPQ-
-PARALHSQFPATTLILLPPLPAIAPRLMPVALTIARYL-
-LSPPPITALLPSCLLGSLSFSCLFTFQTSSLIPLW-
-KIPAPTTTKSCRETFLKW

seq id no 248; SPGCHLGPGDQAAPGLHRPPSPWCHLGAGQQARLGVHR-
-PSSPQCHLGLRLCIRLSFYSGAQRHLCQGYHNPSQQEHS-
-ILNSQPPL

seq id no 249; KPAPGSTAPQPPVSPRPRRPGRPRAPPPPQPMVSPRR-
-RTTGPPWRPPPLQSTMSPPPQALHQAQLLLWCTTAP-
-LPGLPQPQPARALHSQFPATTLILLPPLPAIAPRLMPVA-
-LTIARYLLSPPPITALLPSCLLGSLSFSCLFTFQTS-
-SLIPLWKIPAPTTTKSCRETFLKW

seq id no 250; KPAPGSTAPPQPPVSPRPRRPGRPRAPPPPQPMVSPR-
-RRTTGPPWRPPPLQSTMSPPPQALHQAQLLLWCT-
-TAPLPGLPQPQPARALHSQFPATTLILLPPLPAIAP-
-RLMPVALTIARYLLSPPPITALLPSCLLGSLSFSCLF-
-TFQTSSLIPLWKIPAPTTTKSCRETFLKW

seq id no 251; KPAPGSTAPPSPGCHLGPGDQAAPGLHRPPSPWCHL-
-GAGQQARLGVHRPSSPQCHLGLRLCIRLSFYSGA-
-QRHLCQGYHNPSQQEHSILNSQPPL

seq id no 252; KPAPGSTAPSPGCHLGPGDQAAPGLHRPPSPWCHL-
-GAGQQARLGVHRPSSPQCHLGLRLCIRLSFYSGAQ-
-RHLCQGYHNPSQQEHSILNSQPPL

seq id no 253; QPMVSPRRRTTGPPWRPPPLQSTMSPPPQALHQAQL-
-LLWCTTAPLPGLPQPQPARALHSQFPATTLILLPPLP-
-AIAPRLMPVALTIARYLLSPPPITALLPSCLLGSL-
-SFSCLFTFQTSSLIPLWKIPAPTTTKSCRETFLKW

seq id no 254; SPWCHLGAGQQARLGVHRPSSPQCHLGLRLCIRLSF-
-YSGAQRHLCQGYHNPSQQEHSILNSQPPL

seq id no 255; RPPPGSTAPQPMVSPRRR

seq id no 256; RPPPGSTAPPQPMVSPRRR

seq id no 257; RPPPGSTAPPSPWCHLGA

seq id no 258; RPPPGSTAPSPWCHLGA

seq id no 259; RPRAPPPPSPWCHL

seq id no 260; RPRAPPPPPSPWC

seq id no 261; RPRAPPPPAHGVTSAP

seq id no 262; RPRAPPPPPAHGV

seq id no 263; APGLHRPPQPMVSP

seq id no 264; AAPGLHRPQPMVSPR

seq id no 265; PGLHRPPPAHGVT

seq id no 266; APGLHRPPAHGVTS

seq id no 267; VDRPQHTEWLSWSNLYRIRHQ

seq id no 268; HYLCTDVAPR

seq id no 269; HYLCTDVAPPR

seq id no 270; HYLCTDVAPPVDRPQHTEWLSWSNLYRIRHQ

seq id no 271; HYLCTDVAPVDRPQHTEWLSWSNLYRIRHQ

seq id no 272; SAYLSPLGTTWLRTCACRLPRPAASCLCTTPSLLW-
-PRRTCPAGSPRATSSPWRMPAPKSCCTTGLAFTS-
-PIGLGWRSATASGYARIWPVLSLTCQSWSTSLPSTAVTW

seq id no 273; PSAYLSPLGTTWLRTCACRLPRPAASCLCTTPSLLWP-
-RRTCPAGSPRATSSPWRMPAPKSCCTTGLAFTSP-
-IGLGWRSATASGYARIWPVLSLTCQSWSTSLPSTAVTW

seq id no 274; PAPIFLLWGPLG

seq id no 275; APIFLLWGPLG

seq id no 276; LPARAPGPPSAYLSPLGTTWLRTCACRLPRPAASCL-
-CTTPSLLWPRRTCPAGSPRATSSPWRMPAPKSCC-
-TTGLAFTSPIGLGWRSATASGYARIWPVLSLT-
-CQSWSTSLPSTAVTW

seq id no 277; LPARAPGPPPSAYLSPLGTTWLRTCACRLPRPAAS-
-CLCTTPSLLWPRRTCPAGSPRATSSPWRMPAPKSCC-
-TTGLAFTSPIGLGWRSATASGYARIWPVLSLTC-
-QSWSTSLPSTAVTW

seq id no 278; LPARAPGPPPAPIFLLWGPLG

seq id no 279; LPARAPGPPAPIFLLWGPLG

seq id no 280; DLEHHGGVTRHRHR

seq id no 281; LVSDYSMTPRP

seq id no 282; LVSDYSMTPPRP

seq id no 283; LVSDYSMTPPDLEHHGGVTRHRHR

seq id no 284; LVSDYSMTPDLEHHGGVTRHRHR

seq id no 285; FHHIATDVGPFVRIGFLKIKGKIKGKSLRKPNW-
-KTQHKLKRALMFLIVKKL

seq id no 286; PFHHIATDVGPFVRIGFLKIKGKIKGKSLRKPNWK-
-TQHKLKRALMFLIVKKL

seq id no 287; PSITLQQMLAPS

seq id no 298; SITLQQMLAPS

seq id no 289; TSCNEMNPPFHHIATDVGPFVRIGFLKIKGKIKGKSL-
-RKPNWKTQHKLKRALMFLIVKKL

seq id no 290; TSCNEMNPPPFHHIATDVGPFVRIGFLKIKGKIKG-
-KSLRKPNWKTQHKLKRALMFLIVKKL

seq id no 291; TSCNEMNPPSITLQQMLAPS

seq id no 292; TSCNEMNPPPSITLQQMLAPS

seq id no 293; LEMILFLMTF

seq id no 294; HPCITKTFLEMILFLMTF

seq id no 295; HPCITKTFFLEMILFLMTF

seq id no 296; HPCITKTFFWR

seq id no 297; HPCITKTFWR

seq id no 298; LMFEHSQMRLNSKNAHLPIISF

seq id no 299; EYGSIIAFLMFEHSQMRLNSKNAHLPIISF

seq id no 300; EYGSIIAFFLMFEHSQMRLNSKNAHLPIISF

seq id no 301; HLNKGRRLGDKIRAT

seq id no 302; FHLNKGRRLGDKIRAT

seq id no 303; VTSGTPFFHLNKGRRLGDKIRAT

seq id no 304; VTSGTPFFFHLNKGRRLGDKIRAT

seq id no 305; VTSGTPFFFI

seq id no 306; VTSGTPFFI

seq id no 307; CEIERIHFFF

seq id no 308; CEIERIHFFSK

seq id no 309; CEIERIHFSK

seq id no 310; FRYISKSI

seq id no 311; RYISKSI

seq id no 312; FKKYEPIFFRYISKSI

seq id no 313; FKKYEPIFRYISKSI

seq id no 314; FPDSDQPGPLYPLDPSCLISSASNPQELSDCHYIH-
-LAFGFSNWRSCPVLPGHCGVQ

seq id no 315; PDSDQPGPLYPLDPSCLISSASNPQELSDCHYIHL-
-AFGFSNWRSCPVLPGHCGVQ

seq id no 316; LNMFASVFS

seq id no 317; LNMFASVFFS

seq id no 318; LNMFASVFFPDSDQPGPLYPLDPSCLISSASNPQE-
-LSDCHYIHLAFGFSNWRSCPVLPGHCGVQ

seq id no 319; LNMFASVFPDSDQPGPLYPLDPSCLISSASNPQELS-
-DCHYIHLAFGFSNWRSCPVLPGHCGVQ

seq id no 320; AMEETVVVAVATVETEVEAMEETGVVAAMEETEVGAT-
-EETEVAMEAKWEEETTTEMISATDHT

seq id no 321; LWVRPWLWEWLRWRPKWRLWRRQEWWRLWRRPRWGL-
-RRRPRWLWRENGRKKRLQK

seq id no 322; YGGDRSRGAMEETVVVAVATVETEVEAMEETGVVAAM-
-EETEVGATEETEVAMEAKWEEETTTEMISATDHT

seq id no 323; YGGDRSRGGAMEETVVVAVATVETEVEAMEETGVVA-
-AMEETEVGATEETEVAMEAKWEEETTTEMISATDHT

seq id no 324; YGGDRSRGGLWVRPWLWEWLRWEPKWRLWRRQEWW-
-RLWRRPRWGLRRRPRWLWRENGRKKRLQK

seq id no 325; YGGDRSRGLWVRPWLWEWLRWEPKWRLWRRQEWWR-
-LWRRPRWGLRRRPRWLWRENGRKKRLQK

seq id no 326; EFGGGRRQK

seq id no 327; EFGGRRQK

seq id no 328; RRAKGGGAGASNPRQ

seq id no 329; GRRAKGGGAGASNPRQ

seq id no 330; DVGLREGALELPTRGNKRNVA

seq id no 331; MRGGGGVGGRRAKGGGAGASNPRQ

seq id no 332; MRGGGGVGGGRRAKGGGAGASNPRQ

seq id no 333; MRGGGGVGGDVGLREGALELPTRGNKRNVA

seq id no 334; MRGGGGVGDVGLREGALELPTRGNKRNVA

seq id no 335; VWQLAGPMLAGWRSLGSWFCRMYGI

seq id no 336; CGSWPALCWRAGGVWAVGSAGCMEYDPEALPAAWGP-
-AAAATVHPRR

seq id no 337; RRYPCEWGVWQLAGPMLAGWRSLGSWFCRMYGI

seq id no 338; RRYPCEWGGVWQLAGPMLAGWRSLGSWFCRMYGI

seq id no 339; RRYPCEWGGCGSWPALCWRAGGVWAVGSAGCMEYD-
-EALPAAWGPAAAATVHPRR

seq id no 340; RRYPCEWGCGSWPALCWRAGGVWAVGSAGCMEYDPE-
-ALPAAWGPAAAATVHPRR

seq id no 341; LWLWAGWTVWWSCGPGEKGHGWPSLPTMALLLLRFSCM-
-RVASY

seq id no 342; GLWLWAGWTVWWSCGPGEKGHGWPSLPTMALLLL-
-RFSCMRVASY

seq id no 343; GCGCGPAGQYGGAVGLARRGTAGCLPCPPWLCCCCAF-
-PACGLPGTDGWRGWQGSGCVRVSGSAPWAPGFPFSP-
-PCPLCGTQPRW

seq id no 344; CGCGPAGQYGGAVGLARRGTAGCLPCPPWLCCCCAFPACG-
-LPGTDGWRGWQGSGCVRVSGSAPWAPGFPFSPPC-
-PLCGTQPRW

seq id no 345; LAFNVPGGLWLWAGWTVWWSCGPGEKGHGWPSLPTMA-
-LLLLRFSCMRVASY

seq id no 346; LAFNVPGGGLWLWAGWTVWWSCGPGEKGHGWPSLPTM-
-ALLLLRFSCMRVASY

seq id no 347; LAFNVPGGGCGCGPAGQYGGAVGLARRGTAGCLPCPP-
-WLCCCCAFPACGLPGTDGWRGWQGSGCVRVSGSAPW-
-APGFPFSPPCPLCGTQPRW

seq id no 348; LAFNVPGGCGCGPAGQYGGAVGLARRGTAGCLPCPPW-
-LCCCCAFPACGLPGTDGWRGWQGSGCVRVSGSAPWA-
-PGFPFSPPCPLCGTQPRW

seq id no 349; PPMPMPGQREAPGRQEA

seq id no 350; GPPMPMPGQREAPGRQEA

seq id no 351; GHQCQCQGKGRHRADRRPDTAQEE

seq id no 352; HQCQCQGKGRHRADRRPDTAQEE

seq id no 353; GGHSYGGGPPMPMPGQREAPGRQEA

seq id no 354; GGHSYGGGGPPMPMPGQREAPGRQEA

seq id no 355; GGHSYGGGGHQCQCQGKGRHRADRRPDTAQEE

seq id no 356; GGHSYGGGHQCQCQGKGRHRADRRPDTAQEE

seq id no 357; APCPQSSGGG

seq id no 358; LPAPSQAAADELDRRPG

seq id no 359; TKVRLIRGAPCPQSSGGG

seq id no 360; TKVRLIRGGAPCPQSSGGG

seq id no 361; TKVRLIRGGLPAPSQAAADELDRRPG

seq id no 362; TKVRLIRGLPAPSQAAADELDRRPG

seq id no 363; CSLAKDGSTEDTVSSLCGEEDTEDEELEAAASHLNK-
-DLYRELLGG

seq id no 364; GCSLAKDGSTEDTVSSLCGEEDTEDEELEAAASHLNK-
-DLYRELLGG

seq id no 365; AAAWQKMAPPRTPRPACVARR

seq id no 366; ENSRPKRGGCSLAKDGSTEDTVSSLCGEEDTEDEELE-
-AAASHLNKDLYRELLGG

seq id no 367; ENSRPKRGGCSLAKDGSTEDTVSSLCGEEDTEDE-
-ELEAAASHLNKDLYRELLGG

seq id no 368; ENSRPKRGGAAAWQKMAPPRTPRPACVARR

seq id no 369; ENSRPKRGAAAWQKMAPPRTPRPACVARR

seq id no 370; HCVLAASGAS

seq id no 371; GHCVLAASGAS

seq id no 372; GTASSRPLGLPKPHLHRPVPIRHPSCPK

seq id no 373; TASSRPLGLPKPHLHRPVPIRHPSCPK

seq id no 374; AGTLQLGGHCVLAASGAS

seq id no 375; AGTLQLGGGHCVLAASGAS

seq id no 376; AGTLQLGGGTASSRPLGLPKPHLHRPVPIRHPSCPK

seq id no 377; AGTLQLGGTASSRPLGLPKPHLHRPVPIRHPSCPK

seq id no 378; RRTPSTEKR

seq id no 379; RRTPSTEKKR

seq id no 380; RRTPSTEKKGRSEC

seq id no 381; RRTPSTEKGRSEC

seq id no 382; STTKCQSGTAETYNSWKVKNLQLEPRRVTSQMNRQVK-
-DMTAILSQS

seq id no 384; SSEEIKKKSTTKCQSGTAETYNSWKVKNLQLEPRRV-
-TSQMNRQVKDMTAILSQS

seq id no 385; SSEEIKKKKSTTKCQSGTAETYNSWKVKNLQLEPRR-
-VTSQMNRQVKDMTAILSQS

seq id no 386; SSEEIKKKKVQPNASQAQQKPTTHGR

seq id no 387; SSEEIKKKVQPNASQAQQKPTTHGR

seq id no 388; NRGWVGAGE

seq id no 389; IEAG

seq id no 390; VHNYCNMKNRGWVGAGE

seq id no 391; VHNYCNMKKNRGWVGAGE

seq id no 392; VHNYCNMKKIEAG

seq id no 393; VHNYCNMKIEAG

seq id no 394; QLRCWNTWAKMFFMVFLIIWQNTMF

seq id no 395; VKKDNHKKQLRCWNTWAKMFFMVFLIIWQNTMF

seq id no 396; VKKDNHKKKQLRCWNTWAKMFFMVFLIIWQNTMF

seq id no 397; VKKDNHKKKNS
seq id no 398; VKKDNHKKNS
seq id no 399; GAEESGPFNRQVQLKVHASGMGRHLWNCPAFWSEV
seq id no 400; HPSPPPEKRS
seq id no 401; HPSPPPEKKRS
seq id no 402; HPSPPPEKKGAEESGPFNRQVQLKVHASGMGRHLW--NCPAFWSEV
seq id no 403; HPSPPPEKGAEESGPFNRQVQLKVHASGMGRHLWN--CPAFWSEV
seq id no 404; MQVLSKTHMNLFPQVLLQMFLRGLKRLLQDLEKSKKRKL
seq id no 405; RCKSARLI
seq id no 406; VQTQPAIKKMQVLSKTHMNLFPQVLLQMFLRGLKRLLQ--DLEKSKKRKL
seq id no 407; VQTQPAIKKKMQVLSKTHMNLFPQVLLQMFLRGLKRL--LQDLEKSKKRKL
seq id no 408; VQTQPAIKKRCKSARLI
seq id no 409; VQTQPAIKRCKSARLI
seq id no 410; ARSGKKQKRKL
seq id no 411; ARSGKKQKKRKL
seq id no 412; ARSGKKQKKENFS
seq id no 413; ARSGKKQKENFS
seq id no 414; KASARSGKSKKRKL
seq id no 415; KASARSGKKSKKRKL
seq id no 416; KASARSGKKAKKENSF
seq id no 417; KASARSGKAKKENSF
seq id no 418; HLNKGRRLGDKIRAT
seq id no 419; VTSGTPFFHLNKGRRLGDKIRAT
seq id no 420; VTSGTPFFFHLNKGRRLGDKIRAT
seq id no 421; VTSGTPFFFI
seq id no 422; VTSGTPFFI
seq id no 423; VTLLYVNTVTLAPNVNMESSRNAHSPATPSAKRK--DPDLTWGGFVFFFCQFH
seq id no 424; KCRCKPNFFVTLLYVNTVTLAPNVNMESSRNAHSP--ATPSAKRKDPDLTWGGFVFFFCQFH
seq id no 425; KCRCKPNFFFVTLLYVNTVTLAPNVNMESSRNAH--SPATPSAKRKDPDLTWGGFVFFFCQFH

seq id no 426; KCRCKPNFFL

seq id no 427; KCRCKPNFL

seq id no 429; LVKKLKEKKMNWIL

seq id no 430; LVKKLKEKKKMNWIL

seq id no 431; LVKKLKEKKR

seq id no 432; LVKKLKEKR

seq id no 433; AAIVKDCCR

seq id no 434; SQPASILGRKL

seq id no 435; SQPASILGKRKL

seq id no 436; SQPASILGKAAIVKDCCR

seq id no 437; SQPASILGAAIVKDCCR

Examples of cancers particularly suitable for treatment with one or a combination of several of this compounds are: colorectal cancer, breast cancer, small-cell lung cancer, non small-cell lung cancer, liver cancer (primary and secondary), renal cancer, melanoma, ovarian cancer, cancer of the brain, head and neck cancer, pancreatic cancer, gastric cancer, eosophageal cancer, prostate cancer and leukemias and lymphomas.

Below are listed some examples of where these mutations may result in gene products that result in development of tumours:

Development of colorectal cancers are believed to result from a series of genetic alterations. Deleted in colorectal cancer (DCC) gene (seq id nos 30-34), Human putative mismatch repair /binding protein (hMSH3) gene (Seq id hos 134-147), Human hMSH6 gene (seq id nos 201-204 and 295-299), Human n-myc gene (seq id nos 190-195), Human TGFβ2 (hTGFβ2) gene (seq id nos 22-29), Human p53 associated gene (seq id nos 287-294) may be involved in colorectal cancer.

Human breast cancer susceptibility (BRCA2) (seq id nos 35-94) and Human BRCA1-associated RING domain protein (BARD1) gene (seq id nos 404-413) are involved in breast cancer and ovarian cancer Human hMSH6 gene (seq id nos 201-204 and 295-299) may be involved in brain tumours.

Gene alteration are frequent in many types of adenocarcinomas , below are listed some genes that are mutated in many cancers:

Human breast cancer susceptibility (BRCA2) gene (seq id nos 35-94),Deleted in colorectal cancer (DCC) gene (seq id nos 30-34),Human putatative mismatch repair/binding protein (hMSH3) gene (seq id nos 134-147), Human hMSH6 gene (seq id nos 201-204 and 295-299), human N-MYC gene (seq id no 190-195), Human TGFb2 (hTGFb2) gene (seq id nos 22-29), Human p53 associated gene (seq id nos 248-267), Human MUC1 gene (seq id nos 248-267), Human germline n-myc gene (seq id nos 184-195), Human Wilm's tumour (WIT-1) associated protein (seq id nos 388-393), Human nasopharynx carcinoma EBV BNLF-1 gene (seq id nos 205-211), Human transforming growth factor-beta inducted gene product (BIGH3) seq id nos 228-233).

Many of the mutated genes may result in development of leukemias and lymphomas: Human neurofibromin (NF1) gene (seq id nos 178-183), b-raf oncogene (seq id nos 172-177), Human protein-tyrosine kinase (JAK1) gene (seq id nos 268-272), Human protein-tyrosine kinase (JAK3) gene (seq id nos 273-280) are examples.

Genes involved in malignant melanoma: Human malignant melanoma metastasis-supressor (hKiSS-1) gene (seq id nos 331-337), Genes involved in metastasis: Human metastasis-assosiated mta1 (hMTA1) gene (seq id nos 360-365).

Cell cycle control and signal transduction is strikcly regulated. Frameshift mutations in these genes may result in uncontrolled cell growth. Examples of genes which may be suseptable are: Human protein tyrosine phosphatase (hPTP) gene (seq id nos 95-102), Human kinase (TTK) gene (seq id nos 109-121), Human transcriptional repressor (CTCF) gene (seq id nos 122-128), Human cell cycle regulatory protein (E1A-binding protein) p300 gene (seq id nos 212-219), Human tranforming growth factor-beta inducted gene product (BIGH3) (seq id nos 228-233), Human FLt4 gene (for transmembrane tyrosinase kinase (seq id nos 281-286), Human G protein-coupled receptor (hGPR1) gene (seq id nos 317-322), Human transcription factor (hITF-2) gene (seq id nos 329-330), Human telomerase-associated protein TP-1 (hTP-1) gene (seq id nos 338-351), Human transcription factor TFIIB 90 kDa subunit (hTFBIIB90) gene (seq id nos 366-373), Human FADD-homologous ICE/CED-3like protease gene (seq id nos 129-133)

Mutations in DNA synthesis or -repair enzymes may also lead to uncontrolled cell growth. Human DNA topoisomerase II (top2) gene (seq id nos 103-108) and Human putative mismatch repair/binding protein (hMSH3) gene (seq id nos 134-147) and (hMSH6) gene (seq id nos 201-204 and 205-299).

The following are tumour suppressor genes, Human retinoblastoma binding protein 1 isoform I (hRBP1) gene (seq id hos 148-158), Human neurofibromin(NF1) gene (seq id nos 178-183), Human p53 associated gene (seq id nos 287-294), Human retinoblastoma related protein (p107) gene (seq id nos 312-316), Human tumour suppressor (hLUCA-1) gene (seq id nos 374-381), Mutations in these genes may result in development of cancer.

The following are oncogenes, proto-oncogenes or putative oncogenes ; Human germline n-myc gene (seq id nos 184-189), Human n-myc gene (seq id nos 190-195), Human can (hCAN) gene (seq id nos 300-302), Human dek (hDEK) gene (seq id nos 309-311), b-raf oncogene (seq id nos 172-177), Human DBL (hDBL) proto-oncogene / Human MCF2PO (hMCF2PO) gene (seq id nos 303-308). Frameshift mutations in these genes may lead to development of cancer.

BIOLOGICAL EXPERIMENTS

Description of the Figures

FIG. 1:
It has been demonstrated that T cells from normal donors can be stimulated with a mixture of peptides containing both mutant BAX and mutant TGFβRII peptides. Peptide mixture dependent T cell proliferation in blood samples from six different donors are shown in figure 1. The results were obtained by stimulating peripheral blood mononuclear cells (PBMCs) from each donor with a mixture of mutant BAX peptides (seq id nos 1,9-12) and mutant TGFβRII peptides (seq id nos 15-21). The concentration of each individual peptide in the mixture was 20 μM. After two weeks, and weekly thereafter, the bulk cultures were restimulated with autologous PBMCs pulsed with 10-25 μM of the peptide mixture. After 4-5 restimulations the bulk cultures were tested in a standard proliferation assay with PBMCs alone or as a control or PBMCs pulsed with 25 μM of the peptides as antigen presenting cells (APCs).

FIG. 2:
It has further been found that T cell clones can be generated against separate peptides of the mixture used in the bulk stimulation experiments. Figure 2 shows the

proliferation of T cell clone 521-2 which was obtained by cloning the bulk culture from donor 1 (figure 1) by seeding 5 cells per well in U-bottomed, 96-well microtiter plates and using autologous PBMCs pulsed with 25 μM of the mutant BAX peptide with seq id no 12 as feeder cells. Autologous B-lymphoblastoid cells were used as APCs in the proliferation assay.

FIG. 3:

In figure three it is shown that mutant BAX peptides and mutant TGFβRII peptides can be used to stimulate T cells (PBMCs) from a patient with breast cancer. Dendritic cells (DCs) from the same cancer patient were used as APCs. The T cell stimulation (figure 3) was obtained by pulsing DCs separately with a mixture of mutant BAX peptides (seq id nos 1,9-12) and a mixture of mutant TGFβRII peptides (seq id nos 15-21) followed by addition of autologous PBMCs and 10 ng/ml tumour necrosis factor. The concentration of each peptide in the mixtures used for pulsing was 25 μM. The PBMCs and the DCs were obtained by leukapheresis from a patient with breast cancer who had been on a granulocyte colony stimulating factor (G-CSF) treatment. The CD34+ cells were isolated from the cell product before DCs were derived using standard methods.

FIG. 4:

Figure 4 shows the capability of T cells obtained from ascites fluid of a pancreatic cancer patient to recognise and proliferate to different synthetic peptides derived from mutant BAX (seq id nos 1,9-12) and mutant TGFβRII (seq id nos 15,17-21). The T cell line was obtained after expansion of T cells present in the ascites fluid of a patient with pancreatic adenocarcinoma. The T cell line was expanded in vitro by culturing with 100 U/ml recombinant

interleukin-2 (rIL-2) (Amersham, Aylesbury, UK) for one week before beeing tested in a proliferation assay.

Autologous, irradiated (30Gy) PBMCs were seeded 5 x 104 in u-bottomed 96-well plates (Costar, Cambridge, MA) and pulsed with single synthetic peptides at 20 µM for 2h. The T cells were added 5 x 104 per well and the plates were incubated for four days at 37°C with addition of 18.5 x 104 Bq/mL 3H-thymidine for the last 12 hours before harvesting. The plates were counted in a liquid scintillation counter (Packard Topcount). Data represent specific proliferation to the different synthetic peptides and values are expressed as the mean of triplicate cultures. These results show that T cells isolated from a pancreatic cancer patient are capable of responding to a panel of peptides carrying amino acid sequences derived from mutant BAX and TGFβRII.

FIG. 5:

Figure 5 further demonstrates the capability T cells from another pancreatic cancer patient to recognise and proliferate to different synthetic peptides derived from mutant BAX and mutant TGFβRII. The T cell line was obtained after expansion of T cells present in the ascites fluid of a patient with pancreatic adencarcinoma. The experiment was set up in the same way as described above. Data represent specific proliferation to the different synthetic peptides and values are expressed as the mean of triplicate cultures.

In order to investigate the T cell response from the latter pancreatic cancer patient, responding T cells were cloned. Peritoneal macrophages were irradiated (30 Gy) and plated 1 x 104 into U-bottomed 96-well plates (Costar) together with 25 µM of each peptide. T cell blasts were counted in a microscope and added 5 blasts per well together with 100 U/ml human recombinant interleukin-2 (rIL-2) (Amersham,

Aylesbury, UK) in a total volume of 200 mL. After 14 days T cell clones were transferred onto 24-well plates (Costar) with 1 mg/mL phytohemagglutinin (PHA, Wellcome, Dartford, UK), 100 U/ml rIL-2 and allogeneic, irradiated PBMCs as feeder cells and screened for peptide specificity after 7 and 14 days.

FIG. 6:

T cell clone 520.5, 520.7 and 520.8 were selected for further characterisation and express the cell surface phenotype CD3+, CD8+ and TcR+. Figure 6 shows the recognition and cytotoxicity of T cell clone 520.5, 520.7 and 520.8 against peptide-pulsed autologous target cells pulsed with the seq id no 10 peptide. Autologous Epstein-barr virus transformed B-cells (EBV) were labelled with 3H-thymidine (9.25 x 104 Bq/ml) over night, washed once and plated 2500 cells per well in 96-well plates with or without 25 mM of synthetic peptide (seq id no 10) and 1% DMSO in medium. After 30 minutes incubation at 37°C the plates were washed before addition of T cells. The plates were further incubated at 37°C for 4 hours and then harvested before counting in a liquid scintillation counter (Packard Topcount). Data represent percent specific lysis of 3H-thymidine labelled peptide pulsed target cells at an effector/target ratio of 10/1. Values are expressed as the mean of triplicate cultures. These results demonstrate that the three different T cell clones obtained from ascites fluid of a pancreatic carcinoma patient, exhibit specific cytotoxicity of autologous EBV targets pulsed with the relevant peptide (seq id no 10) derived from mutant BAX.

FIG. 7:

Figure 7 shows the cytolytic properties of three different T cell clones obtained from the same patient. These T cell clones were cultured and expanded as described above, but they were generated against a synthetic peptide the seq id no 17 peptide carrying amino acid sequences derived from

mutant TGFβRII. T cell clone 538.1, 538.3 and 538.4 all show the cell-surface phenotype CD3+, CD8+ and TcR+. The experimental conditions were as described above (figure 6). Data represent percent specific lysis of 3H-thymidine labelled peptide pulsed target cells pulsed with the seq id no 428 peptide at an effector/target ratio of 10/1. Values are expressed as the mean of triplicate cultures. These results demonstrate that the three different T cell clones obtained from ascites fluid of a pancreatic carcinoma patient, exhibit specific cytotoxicity of autologous EBV targets pulsed with the relevant peptide (seq id no 428) derived from mutant TGFβRII.

Synthesis

The peptides were synthesised by using continuous flow solid phase peptide synthesis. N-a-Fmoc-amino acids with appropriate side chain protection were used. The Fmoc-amino acids were activated for coupling as pentafluorophenyl esters or by using either TBTU or diisopropyl carbodiimide activation prior to coupling. 20% piperidine in DMF was used for selective removal of Fmoc after each coupling. Cleavage from the resin and final removal of side chain protection was performed by 95% TFA containing appropriate scavengers. The peptides were purified and analysed by reversed phase (C18) HPLC. The identity of the peptides was confirmed by using electro-spray mass spectroscopy (Finnigan mat SSQ710).

The peptides used for *in vitro* studies of T cell stimulation were synthesised by this method.

Several other well known methods can be applied by a person skilled in the art to synthesise the peptides.

Examples of the method for determining new frameshift mutation peptides.

In this Example, the BAX gene is used to illustrate the principle.

In each of the steps listed below, the 1st line is the gene sequence and 2nd line is amino acid sequence.
In the steps 2-5, the outlined sequences represent the mutant part of the protein.

Step one:

Normal BAX.

ATG GGG GGG GAG GCA CCC GAG CTG GCC CTG GAC CCG GTG .....
M G G E A P E L A L D P V ...

Step two:

1G deleted from gene sequence.

ATG GGG GGG AGG CAC CCG AGC TGG CCC TGG ACC CGG TGC CTC
M G G R H P S W P W T R C L

AGG ATG CGT CCA CCA AGA AGC TGA
R M R P P R S stop

Step three:

2G deleted from gene sequence.

ATG GGG GGA GGC ACC CGA GCT GGC CCT GGA CCC GGT GCC
M G G G T R A G P G P G A

TCA GGA TGC GTC CAC CAA GAA GCT GAG CGA GTG TCT CAA GCG
S G C V H Q E A E R V S Q A

CAT CGG GGA CGA ACT GGA CAG TAA
H R G R T G Q stop

Step four:

1G inserted in gene sequence.

ATG GGG GGG GGA GGC ACC CGA GCT GGC CCT GGA CCC GGT GCC
M G G G G T R A G P G P G A

TCA GGA TGC GTC CAC CAA GAA GCT GAG CGA GTG TCT CAA GCG
S G C V H Q E A E R V S Q A

CAT CGG GGA CGA ACT GGA CAG TAA
H R G R T G Q stop

Step five:

2G inserted in gene sequence.

ATG GGG GGG GGG AGG CAC CCG AGC TGG CCC TGG ACC CGG TGC
M G G G R H P S W P W T R C

CTC AGG ATG CGT CCA CCA AGA AGC TGA
L R M R P P R S stop

In the next Example, the TGFβRII gene is used to illustrate the principle.

In each of the steps listed below, the 1st line is the gene sequence and 2nd line is amino acid sequence.
In the steps 2-5, the outlined sequences represent the mutant part of the protein.

Step one:

Normal TGFβRII.

GAA AAA AAA AAG CCT GGT GAG ACT TTC TTC ATG TGT TCC....
E K K K P G E T F F M C S...

Step two:

1A deleted from gene sequence.

GAA AAA AAA AGC CTG GTG AGA CTT TCT TCA TGT GTT CCT GTA
E K K S L V R L S S C V P V

GCT CTG ATG AGT GCA ATG ACA ACA TCA TCT TCT CAG AAG AAT
A L M S A M T T S S S Q K N

ATA ACA CCA GCA ATC CTG ACT TGT TGC TAG
I T P A I L T C C stop

Step three:

2A deleted from gene sequence.

GAA AAA AAA GCC TGG TGA
E K K A W stop

Step four:

1A inserted in gene sequence.

GAA AAA AAA AAA GCC TGG TGA
E K K K A W stop

Step five:

2A inserted in gene sequence.

GAA AAA AAA AAA AGC CTG GTG AGA CTT TCT TCA TGT GTT CCT
E K K K S L V R L S S C V P

GTA GCT CTG ATG AGT GCA ATG ACA ACA TCA TCT TCT CAG AAG
V A L M S A M T T S S S Q K

AAT ATA ACA CCA GCA ATC CTG ACT TGT TGC TAG
N I T P A I L T C C stop

Thus the peptides of the invention may be used in a method for the treatment of cancers with cancer cells harbouring genes with frameshift mutations, which treatment comprises administering at least one peptide of

the present invention *in vivo* or *ex vivo* to a human patient in need of such treatment.

In another embodiment the peptides of the invention may be used to vaccinate a human being disposed for cancers with cancer cells harbouring genes with frameshift mutations, by administering at least one peptide of the present invention to said human being.

It is further considered to be an advantage to administer to a human individual a mixture of the peptides of this invention, whereby each of the peptides of the invention can bind to different types of HLA class I and/or class II molecules of the individual.

It is further anticipated that the power of an anticancer vaccine or peptide drug as disclosed in the above mentioned PCT/NO92/00032 application, can be greatly enhanced if the peptides of the present invention were included. Thus in another embodiment of the present invention peptides of the present invention are administered together with, either simultaneously or in optional sequence, with the peptides disclosed in PCT/NO92/00032.

It is considered that the peptides may be administered together, either simultaneously or separately, with compounds such as cytokines and/or growth factors, i.e. interleukin-2 (IL-2), interleukin-12 (IL-12), granulocyte macrophage colony stimulating factor (GM-CSF), Flt-3 ligand or the like in order to strengthen the immune response as known in the art.

The peptides according to the present invention can be used in a vaccine or a therapeutical composition either alone or in combination with other materials, such as for instance standard adjuvants or in the form of a

lipopeptide conjugate which as known in the art can induce high-affinity cytotoxic T lymphocytes, (K. Deres, Nature, Vol.342, (nov.1989)).

The peptides according to the present invention may be useful to include in either a peptide or recombinant fragment based vaccine.

The peptides according to the present invention can be included in pharmaceutical compositions or in vaccines together with usual additives, diluents, stabilisers or the like as known in the art.

According to this invention, a pharmaceutical composition or vaccine may include the peptides alone or in combination with at least one pharmaceutically acceptable carrier or diluent.

Further a vaccine or therapeutical composition can comprise a selection of peptides which are fragments of the mutant proteins arising from insertion or deletion of bases in a repeat sequence of the gene.

Further a vaccine composition can comprise at least one peptide selected for one cancer, which vaccine would be administered to a person carrying a genetic disposition for this particular cancer.

Further a vaccine composition can comprise at least one peptide selected for one cancer, which vaccine would be administered to a person belonging to a high risk group for this particular cancer.

The cancer vaccine according to this invention may further be administered to the population in general for example as a mixture of peptides giving rise to T cell

immunity against various common cancers connected with frameshift mutation genes.

The peptides according to this invention may be administered as single peptides or as a mixture of peptides. Alternatively the peptides may be covalently linked with each other to form larger polypeptides or even cyclic polypeptides.

A cancer therapy according to the present invention may be administered both in vivo or ex vivo having as the main goal the raising of specific T cell lines or clones against the mutant gene product associated with the cancer type with which the patient is afflicted.

Further, the frameshift mutant peptides of this invention may be administered to a patient by various routes including but not limited to subcutaneous, intramuscular, intradermal, intraperitoneal, intravenous or the like. In one embodiment the peptides of this invention are administered intradermally. The peptides may be administered at single or multiple injection sites to a patient in a therapeutically or prophylactically effective amount.

The peptides of this invention may be administered only once or alternatively several times, for instance once a week over a period of 1-2 months with a repeated sequence later all according to the need of the patient being treated.

The peptides of this invention can be administered in an amount in the range of 1 microgram (1 µg) to 1 gram (1g) to an average human patient or individual to be vaccinated. It is preferred to use a smaller dose in the

rage of 1 microgram (1 μg) to 1 milligram (1 mg) for each administration.

The invention further encompasses DNA sequences which encodes a frameshift mutation peptide.

The invention additionally encompasses isolated DNA sequences comprising a DNA sequence encoding at least one frameshift mutant peptide, and administration of such isolated DNA sequences as a vaccine for treatment or prophylaxis of cancers associated with frameshift mutations in the genes.

The peptides according to this invention may be administered to an individual in the form of DNA vaccines. The DNA encoding these peptides may be in the form of cloned plasmid DNA or synthetic oligonucleotide. The DNA may be delivered together with cytokines, such as IL-2, and/or other co-stimulatory molecules. The cytokines and/or co-stimulatory molecules may themselves be delivered in the form of plasmid or oligonucleotide DNA. The response to a DNA vaccine has been shown to be increased by the presence of immunostimulatory DNA sequences (ISS). These can take the form of hexameric motifs containing methylated CpG, according to the formula: 5'-purine-purine-CG-pyrimidine-pyrimidine-3'. Our DNA vaccines may therefore incorporate these or other ISS, in the DNA encoding the peptides, in the DNA encoding the cytokine or other co-stimulatory molecules, or in both. A review of the advantages of DNA vaccination is provided by Tighe et al (1998, *Immunology Today*, 19(2), 89-97).

In one embodiment, the DNA sequence encoding the mutant BAX peptides comprises:

Normal BAX.

ATG GGG GGG GAG GCA CCC GAG CTG GCC CTG GAC CCG GTG .....

1G deleted from BAX gene sequence.

*ATG GGG GGG **AGG** CAC CCG AGC TGG CCC TGG ACC CGG TGC CTC*

***AGG ATG CGT CCA CCA AGA AGC** TGA*

2G deleted from BAX gene sequence.

*ATG GGG **GGA** GGC ACC CGA GCT GGC CCT GGA CCC GGT GCC*

TCA GGA TGC GTC CAC CAA GAA GCT GAG CGA GTG TCT CAA GCG

***CAT CGG GGA CGA ACT GGA CAG** TAA*

1G inserted in BAX gene sequence.

*ATG GGG GGG **GGA** GGC ACC CGA GCT GGC CCT GGA CCC GGT GCC*

TCA GGA TGC GTC CAC CAA GAA GCT GAG CGA GTG TCT CAA GCG

***CAT CGG GGA CGA ACT GGA CAG** TAA*

2G inserted in BAX gene sequence.

*ATG GGG GGG GGG **AGG** CAC CCG AGC TGG CCC TGG ACC CGG TGC*

CTC AGG ATG CGT CCA CCA AGA AGC TGA

In a second embodiment, the DNA sequence encoding the mutant TGFβRII peptides comprises:

Normal TGFβRII gene.

GAA AAA AAA AAG CCT GGT GAG ACT TTC TTC ATG TGT TCC....

1A deleted from TGFβRII gene sequence.

GAA AAA AAA AGC CTG GTG AGA CTT TCT TCA TGT GTT CCT GTA GCT CTG ATG AGT GCA ATG ACA ACA TCA TCT TCT CAG AAG AAT ATA ACA CCA GCA ATC CTG ACT TGT TGC TAG

2A deleted from TGFβRII gene sequence.

GAA AAA AAA GCC TGG TGA

1A inserted in TGFβRII gene sequence.

GAA AAA AAA AAA GCC TGG TGA

2A inserted in TGFβRII gene sequence.

GAA AAA AAA AAA AGC CTG GTG AGA CTT TCT TCA TGT GTT CCT GTA GCT CTG ATG AGT GCA ATG ACA ACA TCA TCT TCT CAG AAG AAT ATA ACA CCA GCA ATC CTG ACT TGT TGC TAG

The invention further encompasses vectors and plasmids comprising a DNA sequence encoding a frameshift mutant peptide. The vectors include, but are not limited to *E.Coli* plasmid, a Listeria vector and recombinant viral vectors. Recombinant viral vectors include, but are not limited to orthopox virus, canary virus, capripox virus, suipox virus, vaccinia, baculovirus, human adenovirus, SV40, bovine papilloma virus and the like comprising the DNA sequence encoding a frameshift mutant peptide.

It is considered that an anticancer treatment or prophylaxis may be achieved also through the

administration of an effective amount of a recombinant virus vector or plasmid comprising at least one insertion site containing a DNA sequence encoding a frameshift mutant peptide to a patient, whereby the patient's antigen presenting cells are turned into host cells for the vector/plasmid and presemtation of HLA/frameshift mutation peptide complex is achieved.

A person skilled in the art will find other possible use combinations with the peptides of this invention, and these are meant to be encompassed by the present claim.

The peptides according to this invention may be produced by conventional processes as known in the art, such as chemical peptide synthesis, recombinant DNA technology or protease cleavage of a protein or peptide encoded by a frameshift mutated gene. One method for chemical synthesis is elucidated in the description below.

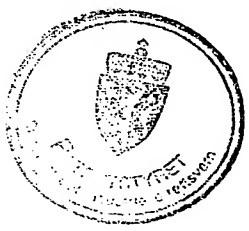
In order for a cancer vaccine and methods for specific cancer therapy based on specific T cell immunity to be effective, three conditions must be met:
1. The peptides used must correspond, either in their full length or after processing by antigen presenting cells, to the processed mutant protein fragment as presented by a HLA Class I and/or class II molecule on the cancer cell or other antigen presenting cells,
2. The peptides used must be bound to a HLA Class I and/or Class II molecule in an immunogenic form, and
3. T-cells capable of recognising and responding to the HLA/peptide complex must be present in the circulation of the human being.

It has been established that all these conditions are met for some representative peptides according to the present invention. The peptides according to the present

invention give rise to specific T cell immune responses *in vitro*. It has been established that the peptides according to this invention correspond to processed mutant protein fragments. This is exemplified with peptides corresponding to fragments of transformed mutant BAX and TGFβRII peptides.

Through the present invention the following advantages are achieved:

- It offers a possibility to treat patients suffering from cancers arising from frame-shift mutations in their genes, most of which cancers known at present do not have any good treatment alternatives.
- It offers a possibility to vaccinate prophylaxtically humans carrying genetic dispositions or belonging to other high risk groups.
- It offers a possibility to prepare a combination treatment for a specific cancer, such as for instance colorectal or pancreatic cancers, wherein the cancer commonly is associated with either a frameshift mutation or a point mutation in the genes.
-Since described frameshift mutations occurs in a large variety of cancers it will be possible to use this peptides in combination with established vaccines and future vaccines to obtain a multiple targetting treatment.
-Likewise patients suffering from cancers associated with multiple frameshift mutations in genes can be treated more efficiently through a combination treatment.



Claims

1. A peptide c h a r a c t e r i s e d in that it

a) is at least 8 amino acids long and is a fragment of a mutant protein arising from a frameshift mutation in a gene of a cancer cell;

and

b) consists of at least one amino acid of the mutant part of a protein sequence encoded by said gene;

and

c) comprises 0-10 amino acids from the carboxyl terminus of the normal part of the protein sequence preceding the amino terminus of the mutant sequence and may further extend to the carboxyl terminus of the mutant part of the protein as determined by a new stop codon generated by the frameshift mutation;

and

d) induces, either in its full length or after processing by antigen presenting cell, T cell responses.

2. A peptide according to claim 1 characterised in that it contain 8-25 amino acids.

3. A peptide according to claim 1 characterised in that it contain 9-20 amino acids.

4. A peptide according to claim 1 characterised in that it contain 9-16 amino acids.

5. A peptide according to claim 1 characterised in that it contain 8-12 amino acids.

6. A peptide according to claim 1 characterised in that it contain 20-25 amino acids.

7. A peptide according to claim 1 characterised in that it contains 9 amino acids.

8. A peptide according to claim 1 characterised in that it contains 12 amino acids.

9. A peptide according to claim 1 characterised in that it contains 13 amino acids.

10. A peptide according to claim 1 characterised in that it is a fragment of a mutant protein encoded by a frameshift mutation in BAX gene or TGFβRII gene.

11. A peptide according to claim 1 characterised in that it is a fragment of a mutant protein encoded by a frameshift mutation in hTGFβ2 gene, DCC gene, BRCA1 gene, BRCA2 gene, hPTP gene, top2 gene, TTK gene, CTCF gene, Human FADD-homologous ICE/CED-3-like protease gene, hMSH3 gene, hRBP1 gene, hFMR1 gene, Human TINUR gene, b-raf oncogene, NF1 gene, Human germline n-myc gene,Human n-myc gene, Human ras inhibitor gene, hMSH6 gene,Human nasopharynx carcinoma EBV BNLF-1 gene, Human cell cycle regulatory protein (E1A-binding protein) p300 gene, bcl-3) gene, BIGH3, Human transcription factor ETV1 gene, IGFBP4 gene,Human MUC1 gene, JAK1 gene, JAK3 gene, Human Flt4 gene, Human p53 associated gene, hCAN gene, hDBL proto-oncogene/hMCF2PO gene, hDEK gene, p107 gene, hGPR1 gene, hRBP56 gene, hITF-2 gene, hKiSS-1 gene, hTP-1 gene, hFDF-5 gene, hMTA1 gene, hTFIIB90 gene, hLUCA-1 gene, Human Wilm's tumour (WIT-1) associated protein, ICErel-III gene, FasL gene,BARD1 gene, hMCF.2 gene, fas gene and Human DPC4 gene.

12. A peptide according to claim 1 characterised in that it is selected from a group of peptides having the following sequence identity numbers:
seq. id. nos. 1-21 and seq id no. 428 or a fragment of any of these.

13. A peptide according to claim 1 characterised in that it is selected from a group of peptides having the following sequence identity numbers:
seq. id. nos. 22-427 and seq. id. nos. 429-437 or a fragment of any of these.

14. A pharmaceutical composition comprising a peptide according to any of the above claims and a pharmaceutically acceptable carrier or diluent.

15. A cancer vaccine comprising a peptide according to any of the claims 1-13 and a pharmaceutically acceptable carrier or diluent.

16. Use of a peptide according to any of the claims 1-13 for the preparation of a pharmaceutical composition for treatment or prophylaxis of cancer.

17. Method for vaccination of a person disposed for or afflicted with cancer, consisting of administering at least one peptide according to the claims 1-13, one or more times, in an amount sufficient for induction of specific T-cell immunity to the mutant proteins or fragments thereof encoded by a frameshift mutated gene.

18. Method according to claim 17 wherein the amount of the peptides is in the range of 1 microgram (1 µg) to 1 gram (1g) and preferentially in the rage of 1 microgram (1 µg) to 1 milligram (1 mg) for each administration.

19. Method for treatment of a patient afflicted with cancer by stimulating in vivo or ex vivo with peptides according to the claims 1-13.

20. Method according to claim 19 wherein the amount of the peptides used is in the range of 1 microgram (1 µg) to 1 gram (1g) and preferentially in the rage of 1 microgram (1 µg) to 1 milligram (1 mg) for each administration.

21. A pharmaceutical composition or vaccine composition comprising a combination of at least one peptide according to claims 1-13 and at least one peptide according to PCT/NO92/00032.

22. A method for identifying new peptides which correspond to fragments of proteins arising from frameshift mutations in genes, characterised by the following steps:

1) identifying a gene in a cancer cell susceptible to frameshift mutation by having a mono nucleoside base repeat sequence of at least five residues, or a di-nucleoside base repeat sequence of at least four di-nucleoside base units;

and

2) removing, respectively, one nucleoside base residue or one di-nucleoside base unit from the repeat sequence and identifying the amino acid sequence of the protein encoded by the altered gene sequence as far as to include a new stop codon;

and/or

3) removing, respectively, two nucleoside base residues or two di-nucleoside base units from the repeat sequence and identifying the amino acid sequence of the protein encoded by the altered gene sequence as far as to include a new stop codon;

and/or

4) inserting, respectively, one nucleoside base residue or one di-nucleoside base unit in the repeat sequence and identifying the amino acid sequence of the protein encoded by the altered gene sequence as far as to include a new stop codon;

and/or

5) inserting, respectively, two nucleoside base residues or two di-nucleoside base units in the repeat sequence and identifying the amino acid sequence of the protein encoded by the altered gene sequence as far as to include a new stop codon.

23. A method according to claim 22, c h a r a c t e r s e d it that it includes the following steps:

6) determining whether the new peptides, either in their full length or as shorter fragments of the peptides, are able to stimulate T cells;

and optionally

7) determining peptides containing nested epitopes for different major HLA class I and/or HLA class II molecules.

24. An isolated DNA sequence comprising a DNA sequence or variants thereof encoding a frameshift mutant peptide according to claim 1.

25. An isolated DNA sequence encoding peptides comprising seq. id. nos. 1-21 and seq. id. no. 428 or variants thereof.

26. An isolated DNA sequence encoding peptides comprising seq. id. nos. 22-427 and seq. id. nos. 429-437 or variants thereof.

27. Use of a DNA sequence according to any of the claims 24-26 for the preparation of a pharmaceutical composition for treatment or prophylaxis of cancer.

28. Method for treatment of a person disposed for or afflicted with cancer, by stimulating *in vivo* or *ex vivo* with DNA sequences according to the claims 24-26.

29. A plasmid or virus vector comprising the DNA sequence of claim 24 encoding a frameshift mutant peptide.

30. A vector according to claim 29 wherein the vector is *E.Coli* plasmid, a Listeria vector and recombinant viral vectors. Recombinant viral vectors include, but are not limited to orthopox virus, canary virus, capripox virus, suipox virus, vaccinia, baculovirus, human adenovirus, SV40 or bovine papilloma virus.

31. Use of a plasmid or virus vector according to claim 29 for the preparation of a pharmaceutical composition for treatment or prophylaxis of cancer.

32. Method for treatment of a person disposed for or afflicted with cancer, by stimulating *in vivo* or *ex vivo* with plasmids or virus vectors according to claim 29.

Abstract

Peptides from oncogene protein products of frameshift mutated genes which eliciting T cellular immunity for use in cancer vaccines and compositions for anticancer treatment .

Sequence identity list

SEQUENCE LISTING

COMMON FOR ALL SEQUENCES.

SEQUENCE TYPE: Peptide

SEQUENCE UNIT: Amino Acid

TOPOLOGY: Linear

SEQUENCE ID NO: 1

SEQUENCE LENGTH: 18 amino acids

R H P S W P W T R C L R M R P P R S

1 5 10 15

SEQUENCE ID NO: 2

SEQUENCE LENGTH: 31 amino acids

G T R A G P G P G A S G C V H Q E A E R V S Q A H R G R T G

1 5 10 15 20 25 30

Q

SEQUENCE ID NO: 3

SEQUENCE LENGTH: 32 amino acids

G G T R A G P G P G A S G C V H Q E A E R V S Q A H R G R T

1 5 10 15 20 25 30

G Q

SEQUENCE ID NO: 4

SEQUENCE LENGTH: 19 amino acids

G R H P S W P W T R C L R M R P P R S

1 5 10 15

SEQUENCE ID NO: 5

SEQUENCE LENGTH: 28 amino acids

I Q D R A G R M G G R H P S W P W T R C L R M R P P R S

1 5 10 15 20 25

SEQUENCE ID NO: 6

SEQUENCE LENGTH: 19 amino acids

I Q D R A G R M G G G R H P S W P W T

1 5 10 15

SEQUENCE ID NO: 7

SEQUENCE LENGTH: 42 amino acids

I Q D R A G R M G G G G T R A G P G P G A S G C V H Q E A E

1 5 10 15 20 25 30

R V S Q A H R G R T G Q

35 40

SEQUENCE ID NO: 8

SEQUENCE LENGTH: 19 amino acids

I Q D R A G R M G G G T R A G P G P G

1 5 10 15

SEQUENCE ID NO: 9

SEQUENCE LENGTH: 22 amino acids

I Q D R A G R M G G R H P S W P W T R C L R

1 5 10 15 20

SEQUENCE ID NO: 10

SEQUENCE LENGTH: 22 amino acids

A S G C V H Q E A E R V S Q A H R G R T G Q

1 5 10 15 20

SEQUENCE ID NO: 11

SEQUENCE LENGTH: 22 amino acids

G G T R A G P G P G A S G C V H Q E A E R V

1 5 10 15 20

SEQUENCE ID NO: 12

SEQUENCE LENGTH: 22 amino acids

I Q D R A G R M G G G G T R A G P G P G A S
1 5 10 15 20

SEQUENCE ID NO: 13

SEQUENCE LENGTH: 34 amino acids

S L V R L S S C V P V A L M S A M T T S S S Q K N I T P A I
1 5 10 15 20 25 30

L T C C

SEQUENCE ID NO: 14

SEQUENCE LENGTH: 44 amino acids

S P K C I M K E K K S L V R L S S C V P V A L M S A M T T S
1 5 10 15 20 25 30

S S Q K N I T P A I L T C C
35 40

SEQUENCE ID NO: 15

SEQUENCE LENGTH: 19 amino acids

P K C I M K E K K K S L V R L S S C V
1 5 10 15

SEQUENCE ID NO: 16

SEQUENCE LENGTH: 23 amino acids

A L M S A M T T S S S Q K N I T P A I L T C C
1 5 10 15 20

SEQUENCE ID NO: 17

SEQUENCE LENGTH: 23 amino acids

S L V R L S S C V P V A L M S A M T T S S S Q
1 5 10 15 20

SEQUENCE ID NO: 18

SEQUENCE LENGTH: 22 amino acids

S P K C I M K E K K S L V R L S S C V P V A
1 5 10 15 20

SEQUENCE ID NO: 19

SEQUENCE LENGTH: 12 amino acids

S P K C I M K E K K A W

1 5 10

SEQUENCE ID NO: 20

SEQUENCE LENGTH: 12 amino acids

P K C I M K E K K K A W

1 5 10

SEQUENCE ID NO: 21

SEQUENCE LENGTH: 19 amino acids

A M T T S S S Q K N I T P A I L T C C

1 5 10 15

SEQUENCE ID NO: 22

SEQUENCE LENGTH: 9 amino acids

T V G R P H I S C

1 5

SEQUENCE ID NO: 23

SEQUENCE LENGTH: 10 amino acids

K T V G R P H I S C

1 5 10

SEQUENCE ID NO: 24

SEQUENCE LENGTH: 18 amino acids

K Q W E D P T S P A N V I A L L Q T

1 5 10 15

SEQUENCE ID NO: 25

SEQUENCE LENGTH: 17 amino acids

Q W E D P T S P A N V I A L L Q T

1 5 10 15

SEQUENCE ID NO: 26

SEQUENCE LENGTH: 19 amino acids

Q K T I K S T R K K T V G R P H I S C

1 5 10 15

SEQUENCE ID NO: 27

SEQUENCE LENGTH: 20 amino acids

Q K T I K S T R K K K T V G R P H I S C

1 5 10 15 20

SEQUENCE ID NO: 28

SEQUENCE LENGTH: 28 amino acids

Q K T I K S T R K K K Q W E D P T S P A N V I A L L Q T

1 5 10 15 20 25

SEQUENCE ID NO: 29

SEQUENCE LENGTH: 27 amino acids

Q K T I K S T R K K Q W E D P T S P A N V I A L L Q T

1 5 10 15 20 25

SEQUENCE ID NO: 30

SEQUENCE LENGTH: 34 amino acids

A A D L Q Q Q F V H F L D C W D V S S I P F T L H L P Q A Q

1 5 10 15 20 25 30

D I T T

SEQUENCE ID NO: 31

SEQUENCE LENGTH: 9 amino acids

G K D A K E K S S

1 5

SEQUENCE ID NO: 32

SEQUENCE LENGTH: 10 amino acids

G K D A K E K K S S

1 5 10

SEQUENCE ID NO: 33

SEQUENCE LENGTH: 42 amino acids

G K D A K E K K A A D L Q Q Q F V H F L D C W D V S S I P F
1 5 10 15 20 25 30
T L H L P Q A Q D I T T
35 40

SEQUENCE ID NO: 34

SEQUENCE LENGTH: 41 amino acids

G K D A K E K A A D L Q Q Q F V H F L D C W D V S S I P F T
1 5 10 15 20 25 30
L H L P Q A Q D I T T
35 40

SEQUENCE ID NO: 35

SEQUENCE LENGTH: 9 amino acids

F S M K Q T L M N V K N L K T K
1 5 10 15

SEQUENCE ID NO: 36

SEQUENCE LENGTH: 17 amino acids

K F S M K Q T L M N V K N L K T K
1 5 10 15

SEQUENCE ID NO: 37

SEQUENCE LENGTH: 25 amino acids

V R T S K T R K K F S M K Q T L M N V K N L K T K
1 5 10 15 20 25

SEQUENCE ID NO: 38

SEQUENCE LENGTH: 26 amino acids

V R T S K T R K K K F S M K Q T L M N V K N L K T K
1 5 10 15 20 25

SEQUENCE ID NO: 39

SEQUENCE LENGTH: 12 amino acids

V R T S K T R K K N F P

1 5 10

SEQUENCE ID NO: 40

SEQUENCE LENGTH: 11 amino acids

V R T S K T R K N F P

1 5 10

SEQUENCE ID NO: 41

SEQUENCE LENGTH: 10 amino acids

I K K K L L Q F Q K

1 5 10

SEQUENCE ID NO: 42

SEQUENCE LENGTH: 11 amino acids

K I K K K L L Q F Q K

1 5 10

SEQUENCE ID NO: 43

SEQUENCE LENGTH: 17 amino acids

K S R R N Y F N F K N N C Q S R L

1 5 10 15

SEQUENCE ID NO: 44

SEQUENCE LENGTH: 16 amino acids

S R R N Y F N F K N N C Q S R L

1 5 10 15

SEQUENCE ID NO: 45

SEQUENCE LENGTH: 18 amino acids

T N L R V I Q K I K K K L L Q F Q K

1 5 10 15

SEQUENCE ID NO: 46

SEQUENCE LENGTH: 19 amino acids

T N L R V I Q K K I K K K L L Q F Q K

1 5 10 15

SEQUENCE ID NO: 47

SEQUENCE LENGTH: 25 amino acids

T N L R V I Q K K S R R N Y F N F K N N C Q S R L

1 5 10 15 20 25

SEQUENCE ID NO: 48

SEQUENCE LENGTH: 24 amino acids

T N L R V I Q K S R R N Y F N F K N N C Q S R L

1 5 10 15 20

SEQUENCE ID NO: 49

SEQUENCE LENGTH: 5 amino acids

K I M I T

1 5

SEQUENCE ID NO: 50

SEQUENCE LENGTH: 12 amino acids

N I D K I P E K I M I T

1 5 10

SEQUENCE ID NO: 51

SEQUENCE LENGTH: 13 amino acids

N I D K I P E K K I M I T

1 5 10

SEQUENCE ID NO: 52

SEQUENCE LENGTH: 5 amino acids

I I N A N

1 5

SEQUENCE ID NO: 53

SEQUENCE LENGTH: 6 amino acids

K I I N A N

1 5

SEQUENCE ID NO: 54

SEQUENCE LENGTH: 13 amino acids

N D K T V S E K I I N A N

1 5 10

SEQUENCE ID NO: 55

SEQUENCE LENGTH: 14 amino acids

N D K T V S E K K I I N A N

1 5 10

SEQUENCE ID NO: 56

SEQUENCE LENGTH: 14 amino acids

N G L E K E Y L M V N Q K E

1 5 10

SEQUENCE ID NO: 57

SEQUENCE LENGTH: 23 amino acids

S Q T S L L E A K N G L E K E Y L M V N Q K E

1 5 10 15 20

SEQUENCE ID NO: 58

SEQUENCE LENGTH: 24 amino acids

S Q T S L L E A K K N G L E K E Y L M V N Q K E

1 5 10 15 20

SEQUENCE ID NO: 59

SEQUENCE LENGTH: 12 amino acids

S Q T S L L E A K K M A

1 5 10

SEQUENCE ID NO: 60

SEQUENCE LENGTH: 11 amino acids

S Q T S L L E A K M A

1 5 10

SEQUENCE ID NO: 61

SEQUENCE LENGTH: 6 amino acids
T L V F P K
1 5

SEQUENCE ID NO: 62
SEQUENCE LENGTH: 7 amino acids
K T L V F P K
1 5

SEQUENCE ID NO: 63
SEQUENCE LENGTH: 14 amino acids
L K N V E D Q K T L V F P K
1 5 10

SEQUENCE ID NO: 64
SEQUENCE LENGTH: 15 amino acids
L K N V E D Q K K T L V F P K
1 5 10 15

SEQUENCE ID NO: 65
SEQUENCE LENGTH: 10 amino acids
L K N V E D Q K K H
1 5 10

SEQUENCE ID NO: 66
SEQUENCE LENGTH: 9 amino acids
L K N V E D Q K H
1 5

SEQUENCE ID NO: 67
SEQUENCE LENGTH: 6 amino acids
K K I Q L Y
1 5

SEQUENCE ID NO: 68
SEQUENCE LENGTH: 7 amino acids

K K K I Q L Y
1 5

SEQUENCE ID NO: 69

SEQUENCE LENGTH: 36 amino acids

R K R F S Y T E Y L A S I I R F I F S V N R R K E I Q N L S
1 5 10 15 20 25 30

S C N F K I
35

SEQUENCE ID NO: 70

SEQUENCE LENGTH: 15 amino acids

L R I V S Y S K K K K I Q L Y
1 5 10 15

SEQUENCE ID NO: 71

SEQUENCE LENGTH: 16 amino acids

L R I V S Y S K K K K K I Q L Y
1 5 10 15

SEQUENCE ID NO: 72

SEQUENCE LENGTH: 45 amino acids

L R I V S Y S K K R K R F S Y T E Y L A S I I R F I F S V N
1 5 10 15 20 25 30

R R K E I Q N L S S C N F K I
35 40 45

SEQUENCE ID NO: 73

SEQUENCE LENGTH: 44 amino acids

L R I V S Y S K R K R F S Y T E Y L A S I I R F I F S V N R
1 5 10 15 20 25
30

R K E I Q N L S S C N F K I
35 40

SEQUENCE ID NO: 74

SEQUENCE LENGTH: 18 amino acids

Q D L P L S S I C Q T I V T I Y W Q

1 5 10 15

SEQUENCE ID NO: 75

SEQUENCE LENGTH: 19 amino acids

K Q D L P L S S I C Q T I V T I Y W Q

1 5 10 15

SEQUENCE ID NO: 76

SEQUENCE LENGTH: 25 amino acids

N R T C P F R L F V R R M L Q F T G N K V L D R P

1 5 10 15 20 25

SEQUENCE ID NO: 77

SEQUENCE LENGTH: 27 amino acids

G F V V S V V K K Q D L P L S S I C Q T I V T I Y W Q

1 5 10 15 20 25

SEQUENCE ID NO: 78

SEQUENCE LENGTH: 28 amino acids

G F V V S V V K K K Q D L P L S S I C Q T I V T I Y W Q

1 5 10 15 20 25

SEQUENCE ID NO: 79

SEQUENCE LENGTH: 34 amino acids

G F V V S V V K K N R T C P F R L F V R R M L Q F T G N K V

1 5 10 15 20 25 30

L D R P

SEQUENCE ID NO: 80

SEQUENCE LENGTH: 33 amino acids

G F V V S V V K N R T C P F R L F V R R M L Q F T G N K V L

1 5 10 15 20 25 30

D R P

SEQUENCE ID NO: 81

SEQUENCE LENGTH: 8 amino acids

Y R K T K N Q N

1 5

SEQUENCE ID NO: 82

SEQUENCE LENGTH: 9 amino acids

K Y R K T K N Q N

1 5

SEQUENCE ID NO: 83

SEQUENCE LENGTH: 10 amino acids

N T E R P K I R T N

1 5 10

SEQUENCE ID NO: 84

SEQUENCE LENGTH: 17 amino acids

D E T F Y K G K K Y R K T K N Q N

1 5 10 15

SEQUENCE ID NO: 85

SEQUENCE LENGTH: 18 amino acids

D E T F Y K G K K K Y R K T K N Q N

1 5 10 15

SEQUENCE ID NO: 86

SEQUENCE LENGTH: 19 amino acids

D E T F Y K G K K N T E R P K I R T N

1 5 10 15

SEQUENCE ID NO: 87

SEQUENCE LENGTH: 18 amino acids

D E T F Y K G K N T E R P K I R T N

1 5 10 15

SEQUENCE ID NO: 88

SEQUENCE LENGTH: 28 amino acids

```
L S I N N Y R F Q M K F Y F R F T S H G S P F T S A N F
1       5         10        15        20        25
```

SEQUENCE ID NO: 89

SEQUENCE LENGTH: 29 amino acids

```
K L S I N N Y R F Q M K F Y F R F T S H G S P F T S A N F
1       5         10        15        20        25
```

SEQUENCE ID NO: 90

SEQUENCE LENGTH: 10 amino acids

```
N S V S T T T G F R
1       5         10
```

SEQUENCE ID NO: 91

SEQUENCE LENGTH: 37 amino acids

```
N I Q L A A T K K L S I N N Y R F Q M K F Y F R F T S H G S
1       5         10        15        20        25        30
P F T S A N F
        35
```

SEQUENCE ID NO: 92

SEQUENCE LENGTH: 38 amino acids

```
N I Q L A A T K K K L S I N N Y R F Q M K F Y F R F T S H G
1       5         10        15        20        25        30
S P F T S A N F
        35
```

SEQUENCE ID NO: 93

SEQUENCE LENGTH: 19 amino acids

```
N I Q L A A T K K N S V S T T T G F R
1       5         10        15
```

SEQUENCE ID NO: 94

SEQUENCE LENGTH: 18 amino acids

N I Q L A A T K N S V S T T T G F R
1 5 10 15

SEQUENCE ID NO: 95

SEQUENCE LENGTH: 18 amino acids

M E H V A P G R M S A S P Q S P T Q
1 5 10 15

SEQUENCE ID NO: 96

SEQUENCE LENGTH: 19 amino acids

K M E H V A P G R M S A S P Q S P T Q
1 5 10 15

SEQUENCE ID NO: 97

SEQUENCE LENGTH: 59 amino acids

K W S T W L Q A E C Q H L H S P Q R S D K P Q Q A G L D Q Q
1 5 10 15 20 25 30
H H C F A L D S S P G P R P V F L Q L L G L M G Q G R H D
35 40 45 50 55

SEQUENCE ID NO: 98

SEQUENCE LENGTH: 58 amino acids

W S T W L Q A E C Q H L H S P Q R S D K P Q Q A G L D Q Q H
1 5 10 15 20 25 30
H C F A L D S S P G P R P V F L Q L L G L M G Q G R H D
35 40 45 50 55

SEQUENCE ID NO: 99

SEQUENCE LENGTH: 26 amino acids

T F S V W A E K M E H V A P G R M S A S P Q S P T Q
1 5 10 15 20 25

SEQUENCE ID NO: 100

SEQUENCE LENGTH: 27 amino acids

T F S V W A E K K M E H V A P G R M S A S P Q S P T Q
1 5 10 15 20 25

SEQUENCE ID NO: 101

SEQUENCE LENGTH: 67 amino acids

```
T F S V W A E K K W S T W L Q A E C Q H L H S P Q R S D K P
1       5         10        15        20        25        30
Q Q A G L D Q Q H H C F A L D S S P G P R P V F L Q L L G L
        35        40        45        50        55        60
M G Q G R H D
        65
```

SEQUENCE ID NO: 102

SEQUENCE LENGTH: 66 amino acids

```
T F S V W A E K W S T W L Q A E C Q H L H S P Q R S D K P Q
1       5         10        15        20        25        30
Q A G L D Q Q H H C F A L D S S P G P R P V F L Q L L G L M
        35        40        45        50        55        60
G Q G R H D
        65
```

SEQUENCE ID NO: 103

SEQUENCE LENGTH: 18 amino acids

```
H K W L K F C L L R L V K E S F H E
1       5         10        15
```

SEQUENCE ID NO: 104

SEQUENCE LENGTH: 19 amino acids

```
K H K W L K F C L L R L V K E S F H E
1       5         10        15
```

SEQUENCE ID NO: 105

SEQUENCE LENGTH: 27 amino acids

```
K G G K A K G K K H K W L K F C L L R L V K E S F H E
1       5         10        15        20        25
```

SEQUENCE ID NO: 106

SEQUENCE LENGTH: 28 amino acids

K G G K A K G K K K H K W L K F C L L R L V K E S F H E
1 5 10 15 20 25

SEQUENCE ID NO: 107
SEQUENCE LENGTH: 13 amino acids
K G G K A K G K K N T N G
1 5 10

SEQUENCE ID NO: 108
SEQUENCE LENGTH: 12 amino acids
K G G K A K G K N T N G
1 5 10

SEQUENCE ID NO: 109
SEQUENCE LENGTH: 8 amino acids
V N N F F K K L
1 5

SEQUENCE ID NO: 110
SEQUENCE LENGTH: 9 amino acids
K V N N F F K K L
1 5

SEQUENCE ID NO: 111
SEQUENCE LENGTH: 16 amino acids
L S Q G N V K K V N N F F K K L
1 5 10 15

SEQUENCE ID NO: 112
SEQUENCE LENGTH: 17 amino acids
L S Q G N V K K K V N N F F K K L
1 5 10 15

SEQUENCE ID NO: 113
SEQUENCE LENGTH: 38 amino acids
G E K N D L Q L F V M S D R R Y K I Y W T V I L L N P C G N

1 5 10 15 20 25 30
L H L K T T S L
35

SEQUENCE ID NO: 114

SEQUENCE LENGTH: 39 amino acids

K G E K N D L Q L F V M S D R R Y K I Y W T V I L L N P C G
1 5 10 15 20 25 30
N L H L K T T S L
35

SEQUENCE ID NO: 115

SEQUENCE LENGTH: 10 amino acids

K G K K M I C S Y S
1 5 10

SEQUENCE ID NO: 116

SEQUENCE LENGTH: 9 amino acids

G K K M I C S Y S
1 5

SEQUENCE ID NO: 117

SEQUENCE LENGTH: 46 amino acids

S S K T F E K K G E K N D L Q L F V M S D R R Y K I Y W T V
1 5 10 15 20 25 30
I L L N P C G N L H L K T T S L
35 40 45

SEQUENCE ID NO: 118

SEQUENCE LENGTH: 47 amino acids

S S K T F E K K K G E K N D L Q L F V M S D R R Y K I Y W T
1 5 10 15 20 25 30
V I L L N P C G N L H L K T T S L
35 30 45

SEQUENCE ID NO: 119

SEQUENCE LENGTH: 18 amino acids

S S K T F E K K K G K K M I C S Y S

1 5 10 15

SEQUENCE ID NO: 120

SEQUENCE LENGTH: 17 amino acids

S S K T F E K K G K K M I C S Y S

1 5 10 15

SEQUENCE ID NO: 121

SEQUENCE LENGTH: 17 amino acids

Q R K P K R A N C V I Q R R A K M

1 5 10 15

SEQUENCE ID NO: 122

SEQUENCE LENGTH: 18 amino acids

K Q R K P K R A N C V I Q R R A K M

1 5 10 15

SEQUENCE ID NO: 123

SEQUENCE LENGTH: 26 amino acids

N K E N Q K E Q T A L L Y R G G Q R C R C V C L R F

1 5 10 15 20 25

SEQUENCE ID NO: 124

SEQUENCE LENGTH: 26 amino acids

P D Y Q P P A K K Q R K P K R A N C V I Q R R A K M

1 5 10 15 20 25

SEQUENCE ID NO: 125

SEQUENCE LENGTH: 27 amino acids

P D Y Q P P A K K K Q R K P K R A N C V I Q R R A K M

1 5 10 15 20 25

SEQUENCE ID NO: 126

SEQUENCE LENGTH: 35 amino acids

P D Y Q P P A K K N K E N Q K E Q T A L L Y R G G Q R C R C
1 5 10 15 20 25 30
V C L R F
35

SEQUENCE ID NO: 127

SEQUENCE LENGTH: 34 amino acids

P D Y Q P P A K N K E N Q K E Q T A L L Y R G G Q R C R C V
1 5 10 15 20 25 30
C L R F

SEQUENCE ID NO: 128

SEQUENCE LENGTH: 7 amino acids

N L S S L L I
1 5

SEQUENCE ID NO: 129

SEQUENCE LENGTH: 5 amino acids

T C L P F
1 5

SEQUENCE ID NO: 130

SEQUENCE LENGTH: 15 amino acids

Q P T F T L R K N L S S L L I
1 5 10 15

SEQUENCE ID NO: 131

SEQUENCE LENGTH: 16 amino acids

Q P T F T L R K K N L S S L L I
1 5 10 15

SEQUENCE ID NO: 132

SEQUENCE LENGTH: 14 amino acids

Q P T F T L R K K T C L P F
1 5 10

SEQUENCE ID NO: 133

SEQUENCE LENGTH: 13 amino acids

```
Q P T F T L R K T C L P F
1       5          10
```

SEQUENCE ID NO: 134

SEQUENCE LENGTH: 31 amino acids

```
R A T F L L S L W E C S L P Q A R L C L I V S R T G L L V Q
1       5          10         15         20         25         30
S
```

SEQUENCE ID NO: 135

SEQUENCE LENGTH: 19 amino acids

```
G Q H F Y W H C G S A A C H R R G C V
1       5          10         15
```

SEQUENCE ID NO: 136

SEQUENCE LENGTH: 39 amino acids

```
K E N V R D K K R A T F L L S L W E C S L P Q A R L C L I V
1       5          10         15         20         25         30
S R T G L L V Q S
          35
```

SEQUENCE ID NO: 137

SEQUENCE LENGTH: 40 amino acids

```
K E N V R D K K K R A T F L L S L W E C S L P Q A R L C L I
1       5          10         15         20         25         30
V S R T G L L V Q S
          35         40
```

SEQUENCE ID NO: 138

SEQUENCE LENGTH: 28 amino acids

```
K E N V R D K K K G Q H F Y W H C G S A A C H R R G C V
1       5          10         15         20         25
```

SEQUENCE ID NO: 139

SEQUENCE LENGTH: 27 amino acids

K E N V R D K K G Q H F Y W H C G S A A C H R R G C V
1 5 10 15 20 25

SEQUENCE ID NO: 140

SEQUENCE LENGTH: 39 amino acids

I T H T R W G I T T W D S W S V R M K A N W I Q A Q Q N K S
1 5 10 15 20 25 30
L I L S P S F T K
35

SEQUENCE ID NO: 141

SEQUENCE LENGTH: 40 amino acids

K I T H T R W G I T T W D S W S V R M K A N W I Q A Q Q N K
1 5 10 15 20 25 30
S L I L S P S F T K
35 40

SEQUENCE ID NO: 142

SEQUENCE LENGTH: 16 amino acids

K L L T P G G E L P H G I L G Q
1 5 10 15

SEQUENCE ID NO: 143

SEQUENCE LENGTH: 15 amino acids

L L T P G G E L P H G I L G Q
1 5 10 15

SEQUENCE ID NO: 144

SEQUENCE LENGTH: 47 amino acids

P P V C E L E K I T H T R W G I T T W D S W S V R M K A N W
1 5 10 15 20 25 30
I Q A Q Q N K S L I L S P S F T K
35 40 45

SEQUENCE ID NO: 145

SEQUENCE LENGTH: 48 amino acids

P P V C E L E K K I T H T R W G I T T W D S W S V R M K A N
1 5 10 15 20 25 30
W I Q A Q Q N K S L I L S P S F T K
35 40 45

SEQUENCE ID NO: 146

SEQUENCE LENGTH: 24 amino acids

P P V C E L E K K L L T P G G E L P H G I L G Q
1 5 10 15 20

SEQUENCE ID NO: 147

SEQUENCE LENGTH: 23 amino acids

P P V C E L E K L L T P G G E L P H G I L G Q
1 5 10 15 20

SEQUENCE ID NO: 148

SEQUENCE LENGTH: 11 amino acids

S L K D E L E K M K I
1 5 10

SEQUENCE ID NO: 149

SEQUENCE LENGTH: 12 amino acids

S L K D E L E K K M K I
1 5 10

SEQUENCE ID NO: 150

SEQUENCE LENGTH: 12 amino acids

L G Q S S P E K K N K N
1 5 10

SEQUENCE ID NO: 151

SEQUENCE LENGTH: 11 amino acids

L G Q S S P E K N K N
1 5 10

SEQUENCE ID NO: 152

SEQUENCE LENGTH: 23 amino acids

R L R R I N G R G S Q I R S R N A F N R S E E

1 5 10 15 20

SEQUENCE ID NO: 153

SEQUENCE LENGTH: 10 amino acids

E P K V K E E K K T

1 5 10

SEQUENCE ID NO: 154

SEQUENCE LENGTH: 11 amino acids

E P K V K E E K K K T

1 5 10

SEQUENCE ID NO: 155

SEQUENCE LENGTH: 32 amino acids

E P K V K E E K K R L R R I N G R G S Q I R S R N A F N R S

1 5 10 15 20 25 30

E E

SEQUENCE ID NO: 156

SEQUENCE LENGTH: 31 amino acids

E P K V K E E K R L R R I N G R G S Q I R S R N A F N R S E

1 5 10 15 20 25 30

E

SEQUENCE ID NO: 157

SEQUENCE LENGTH: 14 amino acids

T F R Y K G K Q H P F F S T

1 5 10

SEQUENCE ID NO: 158

SEQUENCE LENGTH: 10 amino acids

G P N A P E E K N H

1 5 10

SEQUENCE ID NO: 159

SEQUENCE LENGTH: 11 amino acids

G P N A P E E K K N H

1 5 10

SEQUENCE ID NO: 160

SEQUENCE LENGTH: 23 amino acids

G P N A P E E K K T F R Y K G K Q H P F F S T

1 5 10 15 20

SEQUENCE ID NO: 161

SEQUENCE LENGTH: 22 amino acids

G P N A P E E K T F R Y K G K Q H P F F S T

1 5 10 15 20

SEQUENCE ID NO: 162

SEQUENCE LENGTH: 6 amino acids

M Q N T C V

1 5

SEQUENCE ID NO: 163

SEQUENCE LENGTH: 7 amino acids

K M Q N T C V

1 5

SEQUENCE ID NO: 164

SEQUENCE LENGTH: 9 amino acids

K C K I R V F S K

1 5

SEQUENCE ID NO: 165

SEQUENCE LENGTH: 8 amino acids

C K I R V F S K

1 5

SEQUENCE ID NO: 166

SEQUENCE LENGTH: 14 amino acids

F F K R T V Q K M Q N T C V

1 5 10

SEQUENCE ID NO: 167

SEQUENCE LENGTH: 15 amino acids

F F K R T V Q K K M Q N T C V

1 5 10 15

SEQUENCE ID NO: 168

SEQUENCE LENGTH: 17 amino acids

F F K R T V Q K K C K I R V F S K

1 5 10 15

SEQUENCE ID NO: 169

SEQUENCE LENGTH: 16 amino acids

F F K R T V Q K C K I R V F S K

1 5 10 15

SEQUENCE ID NO: 170

SEQUENCE LENGTH: 7 amino acids

L P H Y L A H

1 5

SEQUENCE ID NO: 171

SEQUENCE LENGTH: 8 amino acids

C L I T W L T N

1 5

SEQUENCE ID NO: 172

SEQUENCE LENGTH: 17 amino acids

G S T T G L S A T P L P H Y L A H

1 5 10 15

SEQUENCE ID NO: 173

SEQUENCE LENGTH: 118 amino acids

G S T T G L S A T P P L P H Y L A H
1 5 10 15

SEQUENCE ID NO: 174
SEQUENCE LENGTH: 19 amino acids
G S T T G L S A T P P C L I T W L T N
1 5 10 15

SEQUENCE ID NO: 175
SEQUENCE LENGTH: 18 amino acids
G S T T G L S A T P C L I T W L T N
1 5 10 15

SEQUENCE ID NO: 176
SEQUENCE LENGTH: 9 amino acids
R F A D K P R P N
1 5

SEQUENCE ID NO: 177
SEQUENCE LENGTH: 20 amino acids
D L P T S P D Q T R S G P V H V S V E P
1 5 10 15 20

SEQUENCE ID NO: 178
SEQUENCE LENGTH: 19 amino acids
D S A A G C S G T P R F A D K P R P N
1 5 10 15

SEQUENCE ID NO: 179
SEQUENCE LENGTH: 20 amino acids
D S A A G C S G T P P R F A D K P R P N
1 5 10 15 20

SEQUENCE ID NO: 180
SEQUENCE LENGTH: 31 amino acids
D S A A G C S G T P P D L P T S P D Q T R S G P V H V S V E

1 5 10 15 20 25 30
P

SEQUENCE ID NO: 181

SEQUENCE LENGTH: 30 amino acids

D S A A G C S G T P D L P T S P D Q T R S G P V H V S V E P
1 5 10 15 20 25 30

SEQUENCE ID NO: 182

SEQUENCE LENGTH: 53 amino acids

A H P E T P A Q N R L R I P C S R R E V R S R A C K P P G A
1 5 10 15 20 25 30
Q G S D E R R G K A S P G R D C D V R T G R P
35 40 45 50

SEQUENCE ID NO: 183

SEQUENCE LENGTH: 54 amino acids

P A H P E T P A Q N R L R I P C S R R E V R S R A C K P P G
1 5 10 15 20 25 30
A Q G S D E R R G K A S P G R D C D V R T G R P
35 40 45 50

SEQUENCE ID NO: 184

SEQUENCE LENGTH: 20 amino acids

R P T R R H P R R I A S G S P A V G G R
1 5 10 15 20

SEQUENCE ID NO: 185

SEQUENCE LENGTH: 63 amino acids

V A I R G H P R P P A H P E T P A Q N R L R I P C S R R E V
1 5 10 15 20 25 30
R S R A C K P P G A Q G S D E R R G K A S P G R D C D V R T
35 40 45 50 55 60
G R P

SEQUENCE ID NO: 186

SEQUENCE LENGTH: 64 amino acids

V A I R G H P R P P P A H P E T P A Q N R L R I P C S R R E

1 5 10 15 20 25 30

V R S R A C K P P G A Q G S D E R R G K A S P G R D C D V R

35 40 45 50 55 60

T G R P

SEQUENCE ID NO: 187

SEQUENCE LENGTH: 30 amino acids

V A I R G H P R P P R P T R R H P R R I A S G S P A V G G R

1 5 10 15 20 25 30

SEQUENCE ID NO: 188

SEQUENCE LENGTH: 29 amino acids

V A I R G H P R P R P T R R H P R R I A S G S P A V G G R

1 5 10 15 20 25

SEQUENCE ID NO: 189

SEQUENCE LENGTH: 85 amino acids

R G R T S G R S L S C C R R P R C R P A V A S R S T A P S P

1 5 10 15 20 25 30

R A G S R R C C L R T S C G A A R P R R T R S A C G D W V A

35 40 45 50 55 60

S P P T R S S S R T A C G A A S P P A R S W S A P

65 70 75 80 85

SEQUENCE ID NO: 190

SEQUENCE LENGTH: 8 amino acids

G G G H L E E V

1 5

SEQUENCE ID NO: 191

SEQUENCE LENGTH: 94 amino acids

Y F G G P D S T P R G R T S G R S L S C C R R P R C R P A V

1 5 10 15 20 25 30

A S R S T A P S P R A G S R R C C L R T S C G A A R P R R T

```
          35          40          45          50          55          60
R S A C G D W V A S P P T R S S S R T A C G A A S P P A R S
          65          70          75          80          85          90
W S A P
```

SEQUENCE ID NO: 192

SEQUENCE LENGTH: 95 amino acids

```
Y F G G P D S T P P R G R T S G R S L S C C R R P R C R P A
1         5          10          15          20          25          30
V A S R S T A P S P R A G S R R C C L R T S C G A A R P R R
          35          40          45          50          55          60
T R S A C G D W V A S P P T R S S S R T A C G A A S P P A R
          65          70          75          80          85          90
S W S A P
          95
```

SEQUENCE ID NO: 193

SEQUENCE LENGTH: 18 amino acids

```
Y F G G P D S T P P G G G H L E E V
1         5          10          15
```

SEQUENCE ID NO: 194

SEQUENCE LENGTH: 17 amino acids

```
Y F G G P D S T P G G G H L E E V
1         5          10          15
```

SEQUENCE ID NO: 195

SEQUENCE LENGTH: 6 amino acids

```
H R V A D P
1         5
```

SEQUENCE ID NO: 196

SEQUENCE LENGTH: 13 amino acids

```
L S Q S S E L D P P S S R
1         5          10
```

SEQUENCE ID NO: 197

SEQUENCE LENGTH: 14 amino acids

L S Q S S E L D P P P S S R

1 5 10

SEQUENCE ID NO: 198

SEQUENCE LENGTH: 16 amino acids

L S Q S S E L D P P H R V A D P

1 5 10 15

SEQUENCE ID NO: 199

SEQUENCE LENGTH: 15 amino acids

L S Q S S E L D P H R V A D P

1 5 10 15

SEQUENCE ID NO: 200

SEQUENCE LENGTH: 11 amino acids

V I L L P E D T P P S

1 5 10

SEQUENCE ID NO: 201

SEQUENCE LENGTH: 12 amino acids

V I L L P E D T P P P S

1 5 10

SEQUENCE ID NO: 202

SEQUENCE LENGTH: 14 amino acids

V I L L P E D T P P L L R A

1 5 10

SEQUENCE ID NO: 203

SEQUENCE LENGTH: 13 amino acids

V I L L P E L D P L L R A

1 5 10

SEQUENCE ID NO: 204

SEQUENCE LENGTH: 5 amino acids

P S P L P

1 5

SEQUENCE ID NO: 205

SEQUENCE LENGTH: 25 amino acids

P L L F H R P C S P S P A L G A T V L A V Y R Y E

1 5 10 15 20 25

SEQUENCE ID NO: 206

SEQUENCE LENGTH: 24 amino acids

L L F H R P C S P S P A L G A T V L A V Y R Y E

1 5 10 15 20

SEQUENCE ID NO: 207

SEQUENCE LENGTH: 13 amino acids

A P R P P L G P P S P L P

1 5 10

SEQUENCE ID NO: 208

SEQUENCE LENGTH: 14 amino acids

A P R P P L G P P P S P L P

1 5 10

SEQUENCE ID NO: 209

SEQUENCE LENGTH: 34 amino acids

A P R P P L G P P P L L F H R P C S P S P A L G A T V L A V

1 5 10 15 20 25 30

Y R Y E

SEQUENCE ID NO: 210

SEQUENCE LENGTH: 33 amino acids

A P R P P L G P P L L F H R P C S P S P A L G A T V L A V Y

1 5 10 15 20 25 30

R Y E

SEQUENCE ID NO: 211

SEQUENCE LENGTH: 28 amino acids

```
T Q V L P Q G C S L S L L H T T F P H R Q V P H I L D W
1       5         10        15        20        25
```

SEQUENCE ID NO: 212

SEQUENCE LENGTH: 29 amino acids

```
P T Q V L P Q G C S L S L L H T T F P H R Q V P H I L D W
1       5         10        15        20        25
```

SEQUENCE ID NO: 213

SEQUENCE LENGTH: 54 amino acids

```
P L Q S F P K D A A S A F S T P R F P T D K F P T S W T G S
1       5         10        15        20        25        30
C P G Q P H G T R A F C Q P G P E F N A F S A C
        35        40        45        50
```

SEQUENCE ID NO: 214

SEQUENCE LENGTH: 53 amino acids

```
L Q S F P K D A A S A F S T P R F P T D K F P T S W T G S C
1       5         10        15        20        25        30
P G Q P H G T R A F C Q P G P E F N A F S A C
        35        40        45        50
```

SEQUENCE ID NO: 215

SEQUENCE LENGTH: 38 amino acids

```
P S P R P Q S Q P P T Q V L P Q G C S L S L L H T T F P H R
1       5         10        15        20        25        30
Q V P H I L D W
        35
```

SEQUENCE ID NO: 216

SEQUENCE LENGTH: 39 amino acids

```
P S P R P Q S Q P P P T Q V L P Q G C S L S L L H T T F P H
1       5         10        15        20        25        30
```

R Q V P H I L D W
35

SEQUENCE ID NO: 217

SEQUENCE LENGTH: 64 amino acids

P S P R P Q S Q P P P L Q S F P K D A A S A F S T P R F P T
1 5 10 15 20 25 30
D K F P T S W T G S C P G Q P H G T R A F C Q P G P E F N A
35 40 45 50 55 60
F S A C

SEQUENCE ID NO: 218

SEQUENCE LENGTH: 63 amino acids

P S P R P Q S Q P P L Q S F P K D A A S A F S T P R F P T D
1 5 10 15 20 25 30
K F P T S W T G S C P G Q P H G T R A F C Q P G P E F N A F
35 40 45 50 55 60
S A C

SEQUENCE ID NO: 219

SEQUENCE LENGTH: 30 amino acids

T A W P G R R R F T T P E P Y C L C T P L G P W A P R F L W
1 5 10 15 20 25 30

SEQUENCE ID NO: 220

SEQUENCE LENGTH: 31 amino acids

P T A W P G R R R F T T P E P Y C L C T P L G P W A P R F L W
1 5 10 15 20 25 30

SEQUENCE ID NO: 221

SEQUENCE LENGTH: 50 amino acids

P R P G P A G G A L L P R S L T A F V P H S G H G L P V S S
1 5 10 15 20 25 30
G E P A Y T P I P H D V P H G T P P F C
35 40 45 50

SEQUENCE ID NO: 222

SEQUENCE LENGTH: 49 amino acids

```
R P G P A G G A L L P R S L T A F V P H S G H G L P V S S G
1       5         10        15        20        25        30
E P A Y T P I P H D V P H G T P P F C
        35        40        45
```

SEQUENCE ID NO: 223

SEQUENCE LENGTH: 39 amino acids

```
D L P A V P G P P T A W P G R R R F T T P E P Y C L C T P L
1       5         10        15        20        25        30
G P W A P R F L W
        35
```

SEQUENCE ID NO: 224

SEQUENCE LENGTH: 40 amino acids

```
D L P A V P G P P P T A W P G R R R F T T P E P Y C L C T P
1       5         10        15        20        25        30
L G P W A P R F L W
        35        40
```

SEQUENCE ID NO: 225

SEQUENCE LENGTH: 59 amino acids

```
D L P A V P G P P P R P G P A G G A L L P R S L T A F V P H
1       5         10        15        20        25        30
S G H G L P V S S G E P A Y T P I P H D V P H G T P P F C
        35        40        45        50        55
```

SEQUENCE ID NO: 226

SEQUENCE LENGTH: 58 amino acids

```
D L P A V P G P P R P G P A G G A L L P R S L T A F V P H S
1       5         10        15        20        25        30
G H G L P V S S G E P A Y T P I P H D V P H G T P P F C
        35        40        45        50        55
```

SEQUENCE ID NO: 227

SEQUENCE LENGTH: 8 amino acids

```
Q W G L S W M S
1       5
```

SEQUENCE ID NO: 228

SEQUENCE LENGTH: 14 amino acids

```
N G D C H G C P E G R Q S L
1       5         10
```

SEQUENCE ID NO: 229

SEQUENCE LENGTH: 17 amino acids

```
F T M D R V L T P Q W G L S W M S
1       5         10        15
```

SEQUENCE ID NO: 230

SEQUENCE LENGTH: 18 amino acids

```
F T M D R V L T P P Q W G L S W M S
1       5         10        15
```

SEQUENCE ID NO: 231

SEQUENCE LENGTH: 24 amino acids

```
F T M D R V L T P P N G D C H G C P E G R Q S L
1       5         10        15        20
```

SEQUENCE ID NO: 232

SEQUENCE LENGTH: 23 amino acids

```
F T M D R V L T P N G D C H G C P E G R Q S L
1       5         10        15        20
```

SEQUENCE ID NO: 233

SEQUENCE LENGTH: 115 amino acids

```
H H P A R Q C P H C I M H L Q T Q L I H R N L T G P S Q L T
1       5         10        15        20        25        30
S L H R S P Y Q I A A T P W T T D F A A S F F L N P V T P F
        35        40        45        50        55        60
```

```
L L C R R C Q G K D V L C T N A R C L S Q T S P S H H K A L
        65        70        75        80        85        90
S R T T T Q C M N T T P W L A V R P A K A F P L L
        95       100       105       110       115
```

SEQUENCE ID NO: 234

SEQUENCE LENGTH: 116 amino acids

```
P H H P A R Q C P H C I M H L Q T Q L I H R N L T G P S Q L
1         5        10        15        20        25        30
T S L H R S P Y Q I A A T P W T T D F A A S F F L N P V T P
        35        40        45        50        55        60
F L L C R R C Q G K D V L C T N A R C L S Q T S P S H H K A
        65        70        75        80        85        90
L S R T T T Q C M N T T P W L A V R P A K A F P L L
        95       100       105       110       115
```

SEQUENCE ID NO: 235

SEQUENCE LENGTH: 23 amino acids

```
H T I Q H A S V P T A S C I S K L N S Y T E N
1         5        10        15        20
```

SEQUENCE ID NO: 236

SEQUENCE LENGTH: 126 amino acids

```
P Q V G M R P S N P P H H P A R Q C P H C I M H L Q T Q L I
1         5        10        15        20        25        30
H R N L T G P S Q L T S L H R S P Y Q I A A T P W T T D F A
        35        40        45        50        55        60
A S F F L N P V T P F L L C R R C Q G K D V L C T N A R C L
        65        70        75        80        85        90
S Q T S P S H H K A L S R T T T Q C M N T T P W L A V R P A
        95       100       105       110       115       120
K A F P L L
       125
```

SEQUENCE ID NO: 237

SEQUENCE LENGTH: 127 amino acids

P Q V G M R P S N P P P H H P A R Q C P H C I M H L Q T Q L
1 5 10 15 20 25 30
I H R N L T G P S Q L T S L H R S P Y Q I A A T P W T T D F
35 40 45 50 55 60
A A S F F L N P V T P F L L C R R C Q G K D V L C T N A R C
65 70 75 80 85 90
L S Q T S P S H H K A L S R T T T Q C M N T T P W L A V R P
95 100 105 110 115 120
A K A F P L L
125

SEQUENCE ID NO: 238

SEQUENCE LENGTH: 34 amino acids

P Q V G M R P S N P P H T I Q H A S V P T A S C I S K L N S
1 5 10 15 20 25 30
Y T E N

SEQUENCE ID NO: 239

SEQUENCE LENGTH: 33 amino acids

P Q V G M R P S N P H T I Q H A S V P T A S C I S K L N S Y
1 5 10 15 20 25 30
T E N

SEQUENCE ID NO: 240

SEQUENCE LENGTH: 51 amino acids

W A A R S W C E R R A A A V A P L A P W A W G C P A G C T P
1 5 10 15 20 25 30
P V A A R A C A A T R P E G W R S P C T H
35 40 45 50

SEQUENCE ID NO: 241

SEQUENCE LENGTH: 52 amino acids

P W A A R S W C E R R A A A V A P L A P W A W G C P A G C T
1 5 10 15 20 25 30

P P V A A R A C A A T R P E G W R S P C T H
35 40 45 50

SEQUENCE ID NO: 242

SEQUENCE LENGTH: 74 amino acids

R G L R G A G A R G G L R L L R H L R P G L G D A L R G V H
1 5 10 15 20 25 30
P P L R L G P A L L P A P R G G E A P A H T D A R A R R V H
35 40 45 50 55 60
G A G G D R G H P G P A A L
65 70

SEQUENCE ID NO: 243

SEQUENCE LENGTH: 61 amino acids

E E K L A R C R P P W A A R S W C E R R A A A V A P L A P W
1 5 10 15 20 25 30
A W G C P A G C T P P V A A R A C A A T R P E G W R S P C T H
35 40 45 50 55 60

SEQUENCE ID NO: 244

SEQUENCE LENGTH: 62 amino acids

E E K L A R C R P P P W A A R S W C E R R A A A V A P L A P
1 5 10 15 20 25 30
W A W G C P A G C T P P V A A R A C A A T R P E G W R S P C T H
35 40 45 50 55 60

SEQUENCE ID NO: 245

SEQUENCE LENGTH: 84 amino acids

E E K L A R C R P P R G L R G A G A R G G L R L L R H L R P
1 5 10 15 20 25 30
G L G D A L R G V H P P L R L G P A L L P A P R G G E A P A
35 40 45 50 55 60
H T D A R A R R V H G A G G D R G H P G P A A L
65 70 75 80

SEQUENCE ID NO: 246

SEQUENCE LENGTH: 83 amino acids

```
E E K L A R C R P R G L R G A G A R G G L R L L R H L R P G
1       5         10        15        20        25        30
L G D A L R G V H P P L R L G P A L L P A P R G G E A P A H
        35        40        45        50        55        60
T D A R A R R V H G A G G D R G H P G P A A L
        65        70        75        80
```

SEQUENCE ID NO: 247

SEQUENCE LENGTH: 163 amino acids

```
Q P P V S P R P R R P G R P R A P P P P Q P M V S P R R R T
1       5         10        15        20        25        30
T G P P W R P P P L Q S T M S P P P Q A L H Q A Q L L L W C
        35        40        45        50        55        60
T T A P L P G L P Q P Q P A R A L H S Q F P A T T L I L L P
        65        70        75        80        85        90
P L P A I A P R L M P V A L T I A R Y L L S P P P I T A L L
        95        100       105       110       115       120
P S C L L G S L S F S C L F T F Q T S S L I P L W K I P A P
        125       130       135       140       145       150
T T T K S C R E T F L K W
        155       160
```

SEQUENCE ID NO: 248

SEQUENCE LENGTH: 85 amino acids

```
S P G C H L G P G D Q A A P G L H R P P S P W C H L G A G Q
1       5         10        15        20        25        30
Q A R L G V H R P S S P Q C H L G L R L C I R L S F Y S G A
        35        40        45        50        55        60
Q R H L C Q G Y H N P S Q Q E H S I L N S Q P P L
        65        70        75        80        85
```

SEQUENCE ID NO: 249

SEQUENCE LENGTH: 172 amino acids

```
K P A P G S T A P Q P P V S P R P R R P G R P R A P P P P Q
```

```
1       5         10        15        20        25        30
P M V S P R R R T T G P P W R P P P L Q S T M S P P P Q A L
        35        40        45        50        55        60
H Q A Q L L L W C T T A P L P G L P Q P Q P A R A L H S Q F
        65        70        75        80        85        90
P A T T L I L L P P L P A I A P R L M P V A L T I A R Y L L
        95        100       105       110       115       120
S P P P I T A L L P S C L L G S L S F S C L F T F Q T S S L
        125       130       135       140       145       150
I P L W K I P A P T T T K S C R E T F L K W
        155       160       165       170
```

SEQUENCE ID NO: 250

SEQUENCE LENGTH: 173 amino acids

```
K P A P G S T A P P Q P P V S P R P R R P G R P R A P P P P
1       5         10        15        20        25        30
Q P M V S P R R R T T G P P W R P P P L Q S T M S P P P Q A
        35        40        45        50        55        60
L H Q A Q L L L W C T T A P L P G L P Q P Q P A R A L H S Q
        65        70        75        80        85        90
F P A T T L I L L P P L P A I A P R L M P V A L T I A R Y L
        95        100       105       110       115       120
L S P P P I T A L L P S C L L G S L S F S C L F T F Q T S S
        125       130       135       140       145       150
L I P L W K I P A P T T T K S C R E T F L K W
        155       160       165       170
```

SEQUENCE ID NO: 251

SEQUENCE LENGTH: 65 amino acids

```
K P A P G S T A P P S P G C H L G P G D Q A A P G L H R P P
1       5         10        15        20        25        30
S P W C H L G A G Q Q A R L G V H R P S S P Q C H L G L R L

C I R L S F Y S G A Q R H L C Q G Y H N P S Q Q E H S I L N
        35        40        45        50        55        60
S Q P P L
```

65

SEQUENCE ID NO: 252

SEQUENCE LENGTH: 94 amino acids

```
K P A P G S T A P S P G C H L G P G D Q A A P G L H R P P S
1       5         10        15        20        25        30
P W C H L G A G Q Q A R L G V H R P S S P Q C H L G L R L C
        35        40        45        50        55        60
I R L S F Y S G A Q R H L C Q G Y H N P S Q Q E H S I L N S
        65        70        75        80        85        90
Q P P L
```

SEQUENCE ID NO: 253

SEQUENCE LENGTH: 113 amino acids

```
Q P M V S P R R R T T G P P W R P P P L Q S T M S P P P Q A
1       5         10        15        20        25        30
L H Q A Q L L L W C T T A P L P G L P Q P Q P A R A L H S Q
        35        40        45        50        55        60
F P A T T L I L L P P L P A I A P R L M P V A L T I A R Y L
        65        70        75        80        85        90
L S P P P I T A L L P S C L L G S L S F S C L F T F Q T S S

L I P L W K I P A P T T T K S C R E T F L K W
        95        100       105       110
```

SEQUENCE ID NO: 254

SEQUENCE LENGTH: 65 amino acids

```
S P W C H L G A G Q Q A R L G V H R P S S P Q C H L G L R L
1       5         10        15        20        25        30
C I R L S F Y S G A Q R H L C Q G Y H N P S Q Q E H S I L N
        35        40        45        50        55        60
S Q P P L
        65
```

SEQUENCE ID NO: 255

SEQUENCE LENGTH: 18 amino acids

R P P P G S T A P Q P M V S P R R R

1 5 10 15

SEQUENCE ID NO: 256

SEQUENCE LENGTH: 19 amino acids

R P P P G S T A P P Q P M V S P R R R

1 5 10 15

SEQUENCE ID NO: 257

SEQUENCE LENGTH: 18 amino acids

R P P P G S T A P P S P W C H L G A

1 5 10 15

SEQUENCE ID NO: 258

SEQUENCE LENGTH: 17 amino acids

R P P P G S T A P S P W C H L G A

1 5 10 15

SEQUENCE ID NO: 259

SEQUENCE LENGTH: 14 amino acids

R P R A P P P P S P W C H L

1 5 10

SEQUENCE ID NO: 260

SEQUENCE LENGTH: 13 amino acids

R P R A P P P P P S P W C

1 5 10

SEQUENCE ID NO: 261

SEQUENCE LENGTH: 16 amino acids

R P R A P P P P A H G V T S A P

1 5 10 15

SEQUENCE ID NO: 262

SEQUENCE LENGTH: 13 amino acids

R P R A P P P P P A H G V

1 5 10

SEQUENCE ID NO: 263

SEQUENCE LENGTH: 14 amino acids

A P G L H R P P Q P M V S P

1 5 10

SEQUENCE ID NO: 264

SEQUENCE LENGTH: 15 amino acids

A A P G L H R P Q P M V S P R

1 5 10 15

SEQUENCE ID NO: 265

SEQUENCE LENGTH: 13 amino acids

P G L H R P P P A H G V T

1 5 10

SEQUENCE ID NO: 266

SEQUENCE LENGTH: 14 amino acids

A P G L H R P P A H G V T S

1 5 10

SEQUENCE ID NO: 267

SEQUENCE LENGTH: 21 amino acids

V D R P Q H T E W L S W S N L Y R I R H Q

1 5 10 15 20

SEQUENCE ID NO: 268

SEQUENCE LENGTH: 10 amino acids

H Y L C T D V A P R

1 5 10

SEQUENCE ID NO: 269

SEQUENCE LENGTH: 11 amino acids

H Y L C T D V A P P R
1 5 10

SEQUENCE ID NO: 270

SEQUENCE LENGTH: 31 amino acids

H Y L C T D V A P P V D R P Q H T E W L S W S N L Y R I R H
1 5 10 15 20 25 30
Q

SEQUENCE ID NO: 271

SEQUENCE LENGTH: 30 amino acids

H Y L C T D V A P V D R P Q H T E W L S W S N L Y R I R H Q
1 5 10 15 20 25 30

SEQUENCE ID NO: 272

SEQUENCE LENGTH: 108 amino acids

S A Y L S P L G T T W L R T C A C R L P R P A A S C L C T T
1 5 10 15 20 25 30
P S L L W P R R T C P A G S P R A T S S P W R M P A P K S C
35 40 45 50 55 60
C T T G L A F T S P I G L G W R S A T A S G Y A R I W P V L
65 70 75 80 85 90
S L T C Q S W S T S L P S T A V T W
95 100 105

SEQUENCE ID NO: 273

SEQUENCE LENGTH: 109 amino acids

P S A Y L S P L G T T W L R T C A C R L P R P A A S C L C T
1 5 10 15 20 25 30
T P S L L W P R R T C P A G S P R A T S S P W R M P A P K S
35 40 45 50 55 60
C C T T G L A F T S P I G L G W R S A T A S G Y A R I W P V
65 70 75 80 85 90
L S L T C Q S W S T S L P S T A V T W
95 100 105

SEQUENCE ID NO: 274

SEQUENCE LENGTH: 12 amino acids

```
P A P I F L L W G P L G
1       5         10
```

SEQUENCE ID NO: 275

SEQUENCE LENGTH: 11 amino acids

```
A P I F L L W G P L G
1       5         10
```

SEQUENCE ID NO: 276

SEQUENCE LENGTH: 117 amino acids

```
L P A R A P G P P S A Y L S P L G T T W L R T C A C R L P R
1       5         10        15        20        25        30
P A A S C L C T T P S L L W P R R T C P A G S P R A T S S P
        35        40        45        50        55        60
W R M P A P K S C C T T G L A F T S P I G L G W R S A T A S
        65        70        75        80        85        90
G Y A R I W P V L S L T C Q S W S T S L P S T A V T W
        95        100       105       110       115
```

SEQUENCE ID NO: 277

SEQUENCE LENGTH: 118 amino acids

```
L P A R A P G P P P S A Y L S P L G T T W L R T C A C R L P
1       5         10        15        20        25        30
R P A A S C L C T T P S L L W P R R T C P A G S P R A T S S
        35        40        45        50        55        60
P W R M P A P K S C C T T G L A F T S P I G L G W R S A T A
        65        70        75        80        85        90
S G Y A R I W P V L S L T C Q S W S T S L P S T A V T W
        95        100       105       110       115
```

SEQUENCE ID NO: 278

SEQUENCE LENGTH: 21 amino acids

```
L P A R A P G P P P A P I F L L W G P L G
1       5         10        15        20
```

SEQUENCE ID NO: 279

SEQUENCE LENGTH: 20 amino acids

L P A R A P G P P A P I F L L W G P L G

1 5 10 15 20

SEQUENCE ID NO: 280

SEQUENCE LENGTH: 14 amino acids

D L E H H G G V T R H R H R

1 5 10

SEQUENCE ID NO: 281

SEQUENCE LENGTH: 11 amino acids

L V S D Y S M T P R P

1 5 10

SEQUENCE ID NO: 282

SEQUENCE LENGTH: 12 amino acids

L V S D Y S M T P P R P

1 5 10

SEQUENCE ID NO: 283

SEQUENCE LENGTH: 24 amino acids

L V S D Y S M T P P D L E H H G G V T R H R H R

1 5 10 15 20

SEQUENCE ID NO: 284

SEQUENCE LENGTH: 23 amino acids

L V S D Y S M T P D L E H H G G V T R H R H R

1 5 10 15 20

SEQUENCE ID NO: 285

SEQUENCE LENGTH: 51 amino acids

F H H I A T D V G P F V R I G F L K I K G K I K G K S L R K

1 5 10 15 20 25 30

P N W K T Q H K L K R A L M F L I V K K L

35 40 45 50

SEQUENCE ID NO: 286

SEQUENCE LENGTH: 52 amino acids

seq id no 286;

P F H H I A T D V G P F V R I G F L K I K G K I K G K S L R

1 5 10 15 20 25 30

K P N W K T Q H K L K R A L M F L I V K K L

35 40 45 50

SEQUENCE ID NO: 287

SEQUENCE LENGTH: 12 amino acids

P S I T L Q Q M L A P S

1 5 10

SEQUENCE ID NO: 288

SEQUENCE LENGTH: 11 amino acids

S I T L Q Q M L A P S

1 5 10

SEQUENCE ID NO: 289

SEQUENCE LENGTH: 60 amino acids

T S C N E M N P P F H H I A T D V G P F V R I G F L K I K G

1 5 10 15 20 25 30

K I K G K S L R K P N W K T Q H K L K R A L M F L I V K K L

35 40 45 50 55 60

SEQUENCE ID NO: 290

SEQUENCE LENGTH: 61 amino acids

T S C N E M N P P P F H H I A T D V G P F V R I G F L K I K

1 5 10 15 20 25 30

G K I K G K S L R K P N W K T Q H K L K R A L M F L I V K K

35 40 45 50 55 60

L

SEQUENCE ID NO: 291

SEQUENCE LENGTH: 20 amino acids

T S C N E M N P P S I T L Q Q M L A P S

1 5 10 15 20

SEQUENCE ID NO: 292

SEQUENCE LENGTH: 21 amino acids

T S C N E M N P P P S I T L Q Q M L A P S

1 5 10 15 20

SEQUENCE ID NO: 293

SEQUENCE LENGTH: 10 amino acids

L E M I L F L M T F

1 5 10

SEQUENCE ID NO: 294

SEQUENCE LENGTH: 18 amino acids

H P C I T K T F L E M I L F L M T F

1 5 10 15

SEQUENCE ID NO: 295

SEQUENCE LENGTH: 19 amino acids

H P C I T K T F F L E M I L F L M T F

1 5 10 15

SEQUENCE ID NO: 296

SEQUENCE LENGTH: 11 amino acids

H P C I T K T F F W R

1 5 10

SEQUENCE ID NO: 297

SEQUENCE LENGTH: 10 amino acids

H P C I T K T F W R

1 5 10

SEQUENCE ID NO: 298

SEQUENCE LENGTH: 22 amino acids

L M F E H S Q M R L N S K N A H L P I I S F
1 5 10 15 20

SEQUENCE ID NO: 299

SEQUENCE LENGTH: 30 amino acids

E Y G S I I A F L M F E H S Q M R L N S K N A H L P I I S F
1 5 10 15 20 25 30

SEQUENCE ID NO: 300

SEQUENCE LENGTH: 31 amino acids

E Y G S I I A F F L M F E H S Q M R L N S K N A H L P I I S
1 5 10 15 20 25 30
F

SEQUENCE ID NO: 301

SEQUENCE LENGTH: 15 amino acids

H L N K G R R L G D K I R A T
1 5 10 15

SEQUENCE ID NO: 302

SEQUENCE LENGTH: 16 amino acids

F H L N K G R R L G D K I R A T
1 5 10 15

SEQUENCE ID NO: 303

SEQUENCE LENGTH: 23 amino acids

V T S G T P F F H L N K G R R L G D K I R A T
1 5 10 15 20

SEQUENCE ID NO: 304

SEQUENCE LENGTH: 24 amino acids

V T S G T P F F F H L N K G R R L G D K I R A T
1 5 10 15 20

SEQUENCE ID NO: 305

SEQUENCE LENGTH: 10 amino acids

V T S G T P F F F I
1 5 10

SEQUENCE ID NO: 306
SEQUENCE LENGTH: 9 amino acids
V T S G T P F F I
1 5

SEQUENCE ID NO: 307
SEQUENCE LENGTH: 10 amino acids
C E I E R I H F F F
1 5 10

SEQUENCE ID NO: 308
SEQUENCE LENGTH: 11 amino acids
C E I E R I H F F S K
1 5 10

SEQUENCE ID NO: 309
SEQUENCE LENGTH: 10 amino acids
C E I E R I H F S K
1 5 10

SEQUENCE ID NO: 310
SEQUENCE LENGTH: 8 amino acids
F R Y I S K S I
1 5

SEQUENCE ID NO: 311
SEQUENCE LENGTH: 7 amino acids
R Y I S K S I
1 5

SEQUENCE ID NO: 312
SEQUENCE LENGTH: 16 amino acids
F K K Y E P I F F R Y I S K S I

1 5 10 15

SEQUENCE ID NO: 313

SEQUENCE LENGTH: 15 amino acids

F K K Y E P I F R Y I S K S I

1 5 10 15

SEQUENCE ID NO: 314

SEQUENCE LENGTH: 56 amino acids

F P D S D Q P G P L Y P L D P S C L I S S A S N P Q E L S D

1 5 10 15 20 25 30

C H Y I H L A F G F S N W R S C P V L P G H C G V Q

35 40 45 50 55

SEQUENCE ID NO: 315

SEQUENCE LENGTH: 55 amino acids

P D S D Q P G P L Y P L D P S C L I S S A S N P Q E L S D C

1 5 10 15 20 25 30

H Y I H L A F G F S N W R S C P V L P G H C G V Q

35 40 45 50 55

SEQUENCE ID NO: 316

SEQUENCE LENGTH: 9 amino acids

L N M F A S V F S

1 5

SEQUENCE ID NO: 317

SEQUENCE LENGTH: 10 amino acids

L N M F A S V F F S

1 5 10 15

SEQUENCE ID NO: 318

SEQUENCE LENGTH: 64 amino acids

L N M F A S V F F P D S D Q P G P L Y P L D P S C L I S S A

1 5 10 15 20 25 30

S N P Q E L S D C H Y I H L A F G F S N W R S C P V L P G H

35 40 45 50 55 60

C G V Q

SEQUENCE ID NO: 319

SEQUENCE LENGTH: 63 amino acids

L N M F A S V F P D S D Q P G P L Y P L D P S C L I S S A S

1 5 10 15 20 25 30

N P Q E L S D C H Y I H L A F G F S N W R S C P V L P G H C

35 40 45 50 55 60

G V Q

SEQUENCE ID NO: 320

SEQUENCE LENGTH: 63 amino acids

A M E E T V V V A V A T V E T E V E A M E E T G V V A A M E

1 5 10 15 20 25 30

E T E V G A T E E T E V A M E A K W E E E T T T E M I S A T

35 40 45 50 55 60

D H T

SEQUENCE ID NO: 321

SEQUENCE LENGTH: 55 amino acids

L W V R P W L W E W L R W R P K W R L W R R Q E W W R L W R

1 5 10 15 20 25 30

R P R W G L R R R P R W L W R E N G R K K R L Q K

35 40 45 50 55

SEQUENCE ID NO: 322

SEQUENCE LENGTH: 71 amino acids

Y G G D R S R G A M E E T V V V A V A T V E T E V E A M E E

1 5 10 15 20 25 30

T G V V A A M E E T E V G A T E E T E V A M E A K W E E E T

35 40 45 50 55 60

T T E M I S A T D H T

65 70

SEQUENCE ID NO: 323

SEQUENCE LENGTH: 72 amino acids

```
Y G G D R S R G G A M E E T V V V A V A T V E T E V E A M E
1       5         10        15        20        25        30
E T G V V A A M E E T E V G A T E E T E V A M E A K W E E E
        35        40        45        50        55        60
T T T E M I S A T D H T
        65        70
```

SEQUENCE ID NO: 324

SEQUENCE LENGTH: 64 amino acids

```
Y G G D R S R G G L W V R P W L W E W L R W E P K W R L W R
1       5         10        15        20        25        30
R Q E W W R L W R R P R W G L R R R P R W L W R E N G R K K
        35        40        45        50        55        60
R L Q K
```

SEQUENCE ID NO: 325

SEQUENCE LENGTH: 63 amino acids

```
Y G G D R S R G L W V R P W L W E W L R W E P K W R L W R R
1       5         10        15        20        25        30
Q E W W R L W R R P R W G L R R R P R W L W R E N G R K K R
        35        40        45        50        55        60
L Q K
```

SEQUENCE ID NO: 326

SEQUENCE LENGTH: 9 amino acids

```
E F G G G R R Q K
1       5
```

SEQUENCE ID NO: 327

SEQUENCE LENGTH: 8 amino acids

```
E F G G R R Q K
1       5
```

SEQUENCE ID NO: 328

SEQUENCE LENGTH: 15 amino acids

R R A K G G G A G A S N P R Q

1 5 10 15

SEQUENCE ID NO: 329

SEQUENCE LENGTH: 16 amino acids

G R R A K G G G A G A S N P R Q

1 5 10 15

SEQUENCE ID NO: 330

SEQUENCE LENGTH: 21 amino acids

D V G L R E G A L E L P T R G N K R N V A

1 5 10 15 20

SEQUENCE ID NO: 331

SEQUENCE LENGTH: 24 amino acids

M R G G G G V G G R R A K G G G A G A S N P R Q

1 5 10 15 20

SEQUENCE ID NO: 332

SEQUENCE LENGTH: 25 amino acids

M R G G G G V G G G R R A K G G G A G A S N P R Q

1 5 10 15 20 25

SEQUENCE ID NO: 333

SEQUENCE LENGTH: 30 amino acids

M R G G G G V G G D V G L R E G A L E L P T R G N K R N V A

1 5 10 15 20 25 30

SEQUENCE ID NO: 334

SEQUENCE LENGTH: 29 amino acids

M R G G G G V G D V G L R E G A L E L P T R G N K R N V A

1 5 10 15 20 25

SEQUENCE ID NO: 335

SEQUENCE LENGTH: 25 amino acids

V W Q L A G P M L A G W R S L G S W F C R M Y G I

1 5 10 15 20 25

SEQUENCE ID NO: 336

SEQUENCE LENGTH: 46 amino acids

C G S W P A L C W R A G G V W A V G S A G C M E Y D P E A L

1 5 10 15 20 25 30

P A A W G P A A A A T V H P R R

35 40 45

SEQUENCE ID NO: 337

SEQUENCE LENGTH: 33 amino acids

R R Y P C E W G V W Q L A G P M L A G W R S L G S W F C R M

1 5 10 15 20 25 30

Y G I

SEQUENCE ID NO: 338

SEQUENCE LENGTH: 34 amino acids

R R Y P C E W G G V W Q L A G P M L A G W R S L G S W F C R

1 5 10 15 20 25 30

M Y G I

SEQUENCE ID NO: 339

SEQUENCE LENGTH: 55 amino acids

R R Y P C E W G G C G S W P A L C W R A G G V W A V G S A G

1 5 10 15 20 25 30

C M E Y D P E A L P A A W G P A A A A T V H P R R

35 40 45 50 55

SEQUENCE ID NO: 340

SEQUENCE LENGTH: 54 amino acids

R R Y P C E W G C G S W P A L C W R A G G V W A V G S A G C

1 5 10 15 20 25 30

M E Y D P E A L P A A W G P A A A A T V H P R R

35 40 45 50

SEQUENCE ID NO: 341

SEQUENCE LENGTH: 43 amino acids

```
L W L W A G W T V W W S C G P G E K G H G W P S L P T M A L
1       5         10        15        20        25        30
L L L R F S C M R V A S Y
        35        40
```

SEQUENCE ID NO: 342

SEQUENCE LENGTH: 44 amino acids

```
G L W L W A G W T V W W S C G P G E K G H G W P S L P T M A
1       5         10        15        20        25        30
L L L L R F S C M R V A S Y
        35        40
```

SEQUENCE ID NO: 343

SEQUENCE LENGTH: 84 amino acids

```
G C G C G P A G Q Y G G A V G L A R R G T A G C L P C P P W
1       5         10        15        20        25        30
L C C C C A F P A C G L P G T D G W R G W Q G S G C V R V S
        35        40        45        50        55        60
G S A P W A P G F P F S P P C P L C G T Q P R W
        65        70        75        80
```

SEQUENCE ID NO: 344

SEQUENCE LENGTH: 83 amino acids

```
C G C G P A G Q Y G G A V G L A R R G T A G C L P C P P W L
1       5         10        15        20        25        30
C C C C A F P A C G L P G T D G W R G W Q G S G C V R V S G
        35        40        45        50        55        60
S A P W A P G F P F S P P C P L C G T Q P R W
        65        70        75        80
```

SEQUENCE ID NO: 345

SEQUENCE LENGTH: 51 amino acids

```
L A F N V P G G L W L W A G W T V W W S C G P G E K G H G W
1       5         10        15        20        25        30
P S L P T M A L L L L R F S C M R V A S Y
        35        40        45        50
```

SEQUENCE ID NO: 346

SEQUENCE LENGTH: 52 amino acids

```
L A F N V P G G G L W L W A G W T V W W S C G P G E K G H G
1       5         10        15        20        25        30
W P S L P T M A L L L L R F S C M R V A S Y
        35        40        45        50
```

SEQUENCE ID NO: 347

SEQUENCE LENGTH: 92 amino acids

```
L A F N V P G G G C G C G P A G Q Y G G A V G L A R R G T A
1       5         10        15        20        25        30
G C L P C P P W L C C C C A F P A C G L P G T D G W R G W Q
        35        40        45        50        55        60
G S G C V R V S G S A P W A P G F P F S P P C P L C G T Q P
        65        70        75        80        85        90
R W
```

SEQUENCE ID NO: 348

SEQUENCE LENGTH: 91 amino acids

```
L A F N V P G G C G C G P A G Q Y G G A V G L A R R G T A G
1       5         10        15        20        25        30
C L P C P P W L C C C C A F P A C G L P G T D G W R G W Q G
        35        40        45        50        55        60
S G C V R V S G S A P W A P G F P F S P P C P L C G T Q P R
        65        70        75        80        85        90
W
```

SEQUENCE ID NO: 349

SEQUENCE LENGTH: 17 amino acids

```
P P M P M P G Q R E A P G R Q E A
1       5         10        15
```

SEQUENCE ID NO: 350

SEQUENCE LENGTH: 18 amino acids

G P P M P M P G Q R E A P G R Q E A

1 5 10 15

SEQUENCE ID NO: 351

SEQUENCE LENGTH: 24 amino acids

G H Q C Q C Q G K G R H R A D R R P D T A Q E E

1 5 10 15 20

SEQUENCE ID NO: 352

SEQUENCE LENGTH: 23 amino acids

H Q C Q C Q G K G R H R A D R R P D T A Q E E

1 5 10 15 20

SEQUENCE ID NO: 353

SEQUENCE LENGTH: 25 amino acids

G G H S Y G G G P P M P M P G Q R E A P G R Q E A

1 5 10 15 20 25

SEQUENCE ID NO: 354

SEQUENCE LENGTH: 26 amino acids

G G H S Y G G G G P P M P M P G Q R E A P G R Q E A

1 5 10 15 20 25

SEQUENCE ID NO: 355

SEQUENCE LENGTH: 32 amino acids

G G H S Y G G G G H Q C Q C Q G K G R H R A D R R P D T A Q

1 5 10 15 20 25 30

E E

SEQUENCE ID NO: 356

SEQUENCE LENGTH: 31 amino acids

G G H S Y G G G H Q C Q C Q G K G R H R A D R R P D T A Q E

1 5 10 15 20 25 30

E

SEQUENCE ID NO: 357

SEQUENCE LENGTH: 10 amino acids

A P C P Q S S G G G

1 5 10

SEQUENCE ID NO: 358

SEQUENCE LENGTH: 17 amino acids

L P A P S Q A A A D E L D R R P G

1 5 10 15

SEQUENCE ID NO: 359

SEQUENCE LENGTH: 18 amino acids

T K V R L I R G A P C P Q S S G G G

1 5 10 15

SEQUENCE ID NO: 360

SEQUENCE LENGTH: xx amino acids

TKVRLIRGGAPCPQSSGGG

1 5 10

SEQUENCE ID NO: 361

SEQUENCE LENGTH: 26 amino acids

T K V R L I R G G L P A P S Q A A A D E L D R R P G

1 5 10 15 20 25

SEQUENCE ID NO: 362

SEQUENCE LENGTH: 25 amino acids

T K V R L I R G L P A P S Q A A A D E L D R R P G

1 5 10 15 20 25

SEQUENCE ID NO: 363

SEQUENCE LENGTH: 45 amino acids

C S L A K D G S T E D T V S S L C G E E D T E D E E L E A A

1 5 10 15 20 25 30

A S H L N K D L Y R E L L G G
35 40 45

SEQUENCE ID NO: 364

SEQUENCE LENGTH: 46 amino acids

G C S L A K D G S T E D T V S S L C G E E D T E D E E L E A
1 5 10 15 20 25 30
A A S H L N K D L Y R E L L G G
35 40 45

SEQUENCE ID NO: 365

SEQUENCE LENGTH: 21 amino acids

A A A W Q K M A P P R T P R P A C V A R R
1 5 10 15 20

SEQUENCE ID NO: 366

SEQUENCE LENGTH: 54 amino acids

E N S R P K R G G C S L A K D G S T E D T V S S L C G E E D
1 5 10 15 20 25 30
T E D E E L E A A A S H L N K D L Y R E L L G G
35 40 45 50

SEQUENCE ID NO: 367

SEQUENCE LENGTH: 55 amino acids

E N S R P K R G G G C S L A K D G S T E D T V S S L C G E E
1 5 10 15 20 25 30
D T E D E E L E A A A S H L N K D L Y R E L L G G
35 40 45 50 55

SEQUENCE ID NO: 368

SEQUENCE LENGTH: 30 amino acids

E N S R P K R G G A A A W Q K M A P P R T P R P A C V A R R
1 5 10 15 20 25 30

SEQUENCE ID NO: 369

SEQUENCE LENGTH: 29 amino acids

E N S R P K R G A A A W Q K M A P P R T P R P A C V A R R
1 5 10 15 20 25

SEQUENCE ID NO: 370
SEQUENCE LENGTH: 10 amino acids
H C V L A A S G A S
1 5 10

SEQUENCE ID NO: 371
SEQUENCE LENGTH: 11 amino acids
G H C V L A A S G A S
1 5 10

SEQUENCE ID NO: 372
SEQUENCE LENGTH: 28 amino acids
G T A S S R P L G L P K P H L H R P V P I R H P S C P K
1 5 10 15 20 25

SEQUENCE ID NO: 373
SEQUENCE LENGTH: 27 amino acids
T A S S R P L G L P K P H L H R P V P I R H P S C P K
1 5 10 15 20 25

SEQUENCE ID NO: 374
SEQUENCE LENGTH: 18 amino acids
A G T L Q L G G H C V L A A S G A S
1 5 10 15

SEQUENCE ID NO: 375
SEQUENCE LENGTH: 19 amino acids
A G T L Q L G G G H C V L A A S G A S
1 5 10 15

SEQUENCE ID NO: 376
SEQUENCE LENGTH: 35 amino acids
A G T L Q L G G T A S S R P L G L P K P H L H R P V P I R H

1 5 10 15 20 25 30
P S C P K
35

SEQUENCE ID NO: 377
SEQUENCE LENGTH: 36 amino acids
A G T L Q L G G G T A S S R P L G L P K P H L H R P V P I R
1 5 10 15 20 25 30
H P S C P K
35

SEQUENCE ID NO: 378
SEQUENCE LENGTH: 9 amino acids
R R T P S T E K R
1 5

SEQUENCE ID NO: 379
SEQUENCE LENGTH: 10 amino acids
R R T P S T E K K R
1 5 10

SEQUENCE ID NO: 380
SEQUENCE LENGTH: 14 amino acids
R R T P S T E K K G R S E C
1 5 10

SEQUENCE ID NO: 381
SEQUENCE LENGTH: 13 amino acids
R R T P S T E K G R S E C
1 5 10

SEQUENCE ID NO: 382
SEQUENCE LENGTH: 46 amino acids
S T T K C Q S G T A E T Y N S W K V K N L Q L E P R R V T S
1 5 10 15 20 25 30
Q M N R Q V K D M T A I L S Q S

35 40 45

SEQUENCE ID NO: 383

SEQUENCE LENGTH: 17 amino acids

V Q P N A S Q A Q Q K P T T H G R

1 5 10 15

SEQUENCE ID NO: 384

SEQUENCE LENGTH: 54 amino acids

S S E E I K K K S T T K C Q S G T A E T Y N S W K V K N L Q

1 5 10 15 20 25 30

L E P R R V T S Q M N R Q V K D M T A I L S Q S

35 40 45 50

SEQUENCE ID NO: 385

SEQUENCE LENGTH: 55 amino acids

S S E E I K K K K S T T K C Q S G T A E T Y N S W K V K N L

1 5 10 15 20 25 30

Q L E P R R V T S Q M N R Q V K D M T A I L S Q S

35 40 45 50 55

SEQUENCE ID NO: 386

SEQUENCE LENGTH: 26 amino acids

S S E E I K K K K V Q P N A S Q A Q Q K P T T H G R

1 5 10 15 20 25

SEQUENCE ID NO: 387

SEQUENCE LENGTH: xx amino acids

S S E E I K K K V Q P N A S Q A Q Q K P T T H G R

1 5 10 15 20 25

SEQUENCE ID NO: 388

SEQUENCE LENGTH: 9 amino acids

N R G W V G A G E

1 5

SEQUENCE ID NO: 389

SEQUENCE LENGTH: 4 amino acids

I E A G

1

SEQUENCE ID NO: 390

SEQUENCE LENGTH: 17 amino acids

V H N Y C N M K N R G W V G A G E

1 5 10 15

SEQUENCE ID NO: 391

SEQUENCE LENGTH: 18 amino acids

V H N Y C N M K K N R G W V G A G E

1 5 10 15

SEQUENCE ID NO: 392

SEQUENCE LENGTH: 13 amino acids

V H N Y C N M K K I E A G

1 5 10

SEQUENCE ID NO: 393

SEQUENCE LENGTH: 12 amino acids

V H N Y C N M K I E A G

1 5 10

SEQUENCE ID NO: 394

SEQUENCE LENGTH: 25 amino acids

Q L R C W N T W A K M F F M V F L I I W Q N T M F

1 5 10 15 20 25

SEQUENCE ID NO: 395

SEQUENCE LENGTH: 33 amino acids

V K K D N H K K Q L R C W N T W A K M F F M V F L I I W Q N

1 5 10 15 20 25 30

T M F

SEQUENCE ID NO: 396

SEQUENCE LENGTH: 34 amino acids

V K K D N H K K K Q L R C W N T W A K M F F M V F L I I W Q

1 5 10 15 20 25 30

N T M F

SEQUENCE ID NO: 397

SEQUENCE LENGTH: 11 amino acids

V K K D N H K K K N S

1 5 10

SEQUENCE ID NO: 398

SEQUENCE LENGTH: 10 amino acids

V K K D N H K K N S

1 5 10

SEQUENCE ID NO: 399

SEQUENCE LENGTH: 35 amino acids

G A E E S G P F N R Q V Q L K V H A S G M G R H L W N C P A

1 5 10 15 20 25 30

F W S E V

35

SEQUENCE ID NO: 400

SEQUENCE LENGTH: 10 amino acids

H P S P P P E K R S

1 5 10

SEQUENCE ID NO: 401

SEQUENCE LENGTH: 11 amino acids

H P S P P P E K K R S

1 5 10

SEQUENCE ID NO: 402

SEQUENCE LENGTH: 44 amino acids

H P S P P P E K K G A E E S G P F N R Q V Q L K V H A S G M

1 5 10 15 20 25 30

G R H L W N C P A F W S E V

35 40

SEQUENCE ID NO: 403

SEQUENCE LENGTH: 43 amino acids

H P S P P P E K G A E E S G P F N R Q V Q L K V H A S G M G

1 5 10 15 20 25 30

R H L W N C P A F W S E V

35 40

SEQUENCE ID NO: 404

SEQUENCE LENGTH: 39 amino acids

M Q V L S K T H M N L F P Q V L L Q M F L R G L K R L L Q D

1 5 10 15 20 25 30

L E K S K K R K L

35

SEQUENCE ID NO: 405

SEQUENCE LENGTH: 8 amino acids

R C K S A R L I

1 5

SEQUENCE ID NO: 406

SEQUENCE LENGTH: 48 amino acids

V Q T Q P A I K K M Q V L S K T H M N L F P Q V L L Q M F L

1 5 10 15 20 25 30

R G L K R L L Q D L E K S K K R K L

35 40 45

SEQUENCE ID NO: 407

SEQUENCE LENGTH: 49 amino acids

V Q T Q P A I K K K M Q V L S K T H M N L F P Q V L L Q M F

1 5 10 15 20 25 30

L R G L K R L L Q D L E K S K K R K L

35 40 45

SEQUENCE ID NO: 408

SEQUENCE LENGTH: 17 amino acids

V Q T Q P A I K K R C K S A R L I

1 5 10 15

SEQUENCE ID NO: 409

SEQUENCE LENGTH: 16 amino acids

V Q T Q P A I K R C K S A R L I

1 5 10 15

SEQUENCE ID NO: 410

SEQUENCE LENGTH: 11 amino acids

A R S G K K Q K R K L

1 5 10

SEQUENCE ID NO: 411

SEQUENCE LENGTH: 12 amino acids

A R S G K K Q K K R K L

1 5 10

SEQUENCE ID NO: 412

SEQUENCE LENGTH: 13 amino acids

A R S G K K Q K K E N S F

1 5 10

SEQUENCE ID NO: 413

SEQUENCE LENGTH: 12 amino acids

A R S G K K Q K E N S F

1 5 10

SEQUENCE ID NO: 414

SEQUENCE LENGTH: 14 amino acids

K A S A R S G K S K K R K L

1 5 10

SEQUENCE ID NO: 415

SEQUENCE LENGTH: 15 amino acids

K A S A R S G K K S K K R K L

1 5 10 15

SEQUENCE ID NO: 416

SEQUENCE LENGTH: 16 amino acids

K A S A R S G K K A K K E N S F

1 5 10 15

SEQUENCE ID NO: 417

SEQUENCE LENGTH: 15 amino acids

K A S A R S G K A K K E N S F

1 5 10 15

SEQUENCE ID NO: 418

SEQUENCE LENGTH: 15 amino acids

H L N K G R R L G D K I R A T

1 5 10 15

SEQUENCE ID NO: 419

SEQUENCE LENGTH: 23 amino acids

V T S G T P F F H L N K G R R L G D K I R A T

1 5 10 15 20

SEQUENCE ID NO: 420

SEQUENCE LENGTH: 24 amino acids

V T S G T P F F F H L N K G R R L G D K I R A T

1 5 10 15 20

SEQUENCE ID NO: 421

SEQUENCE LENGTH: 10 amino acids

V T S G T P F F F I

1 5 10

SEQUENCE ID NO: 422

SEQUENCE LENGTH: 9 amino acids

V T S G T P F F I

1 5

SEQUENCE ID NO: 423

SEQUENCE LENGTH: 51 amino acids

V T L L Y V N T V T L A P N V N M E S S R N A H S P A T P S

1 5 10 15 20 25 30

A K R K D P D L T W G G F V F F F C Q F H

35 40 45 50

SEQUENCE ID NO: 424

SEQUENCE LENGTH: 60 amino acids

K C R C K P N F F V T L L Y V N T V T L A P N V N M E S S R

1 5 10 15 20 25 30

N A H S P A T P S A K R K D P D L T W G G F V F F F C Q F H

35 40 45 50 65 60

SEQUENCE ID NO: 425

SEQUENCE LENGTH: 61 amino acids

K C R C K P N F F F V T L L Y V N T V T L A P N V N M E S S

1 5 10 15 20 25 30

R N A H S P A T P S A K R K D P D L T W G G F V F F F C Q F

35 40 45 50 65 60

H

SEQUENCE ID NO: 426

SEQUENCE LENGTH: 10 amino acids

K C R C K P N F F L

1 5 10

SEQUENCE ID NO: 427

SEQUENCE LENGTH: 9 amino acids

K C R C K P N F L

1 5

SEQUENCE ID NO: 428

SEQUENCE LENGTH: 9 amino acids

S L V R L S S C V

1 5

SEQUENCE ID NO: 429

SEQUENCE LENGTH: 14 amino acids

L V K K L K E K K M N W I L

1 5 10

SEQUENCE ID NO: 430

SEQUENCE LENGTH: 15 amino acids

L V K K L K E K K K M N W I L

1 5 10 15

SEQUENCE ID NO: 431

SEQUENCE LENGTH: 10 amino acids

L V K K L K E K K R

1 5 10

SEQUENCE ID NO: 432

SEQUENCE LENGTH: 9 amino acids

L V K K L K E K R

1 5

SEQUENCE ID NO: 433

SEQUENCE LENGTH: 9 amino acids

A A I V K D C C R

1 5

SEQUENCE ID NO: 434

SEQUENCE LENGTH: 11 amino acids

S Q P A S I L G R K L

1 5 10

SEQUENCE ID NO: 435

SEQUENCE LENGTH: xx amino acids

S Q P A S I L G K R K L

1 5 10 15

SEQUENCE ID NO: 436

SEQUENCE LENGTH: 18 amino acids

S Q P A S I L G K A A I V K D C C R

1 5 10 15

SEQUENCE ID NO: 437

SEQUENCE LENGTH: 17 amino acids

S Q P A S I L G A A I V K D C C R

1 5 10 15

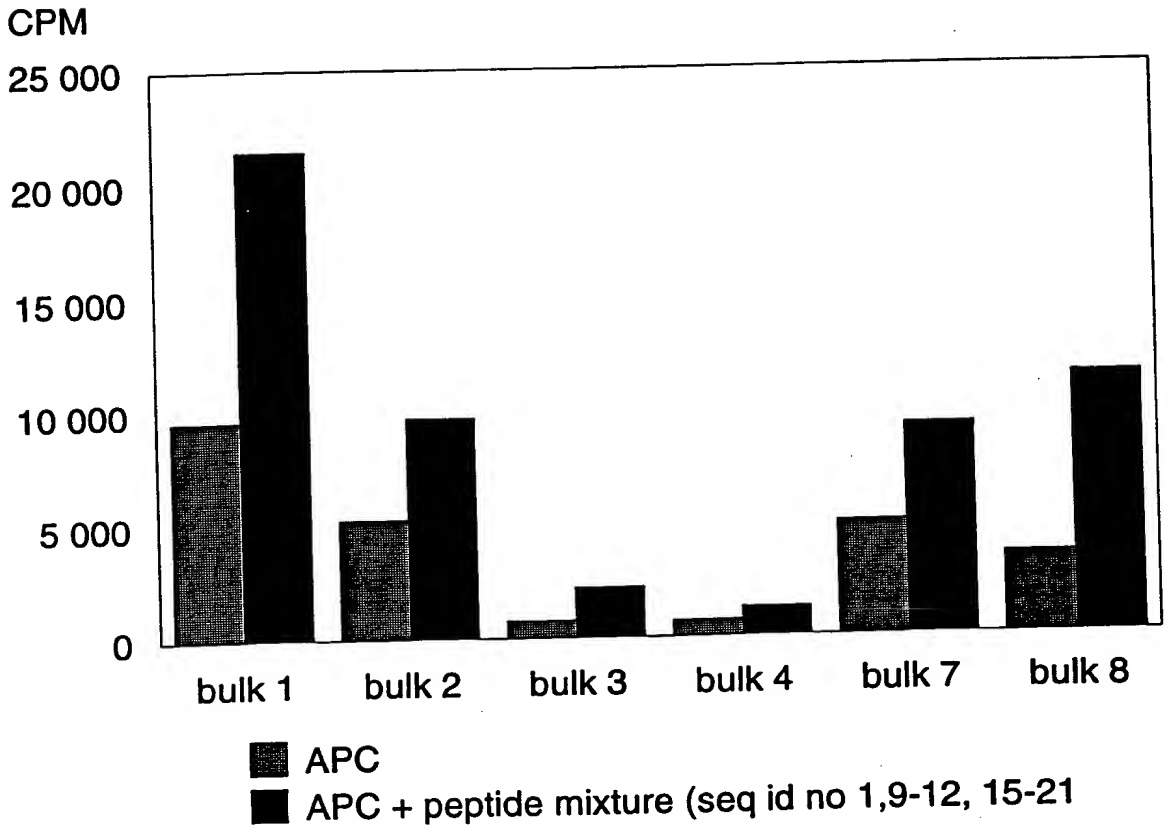


Fig. 1

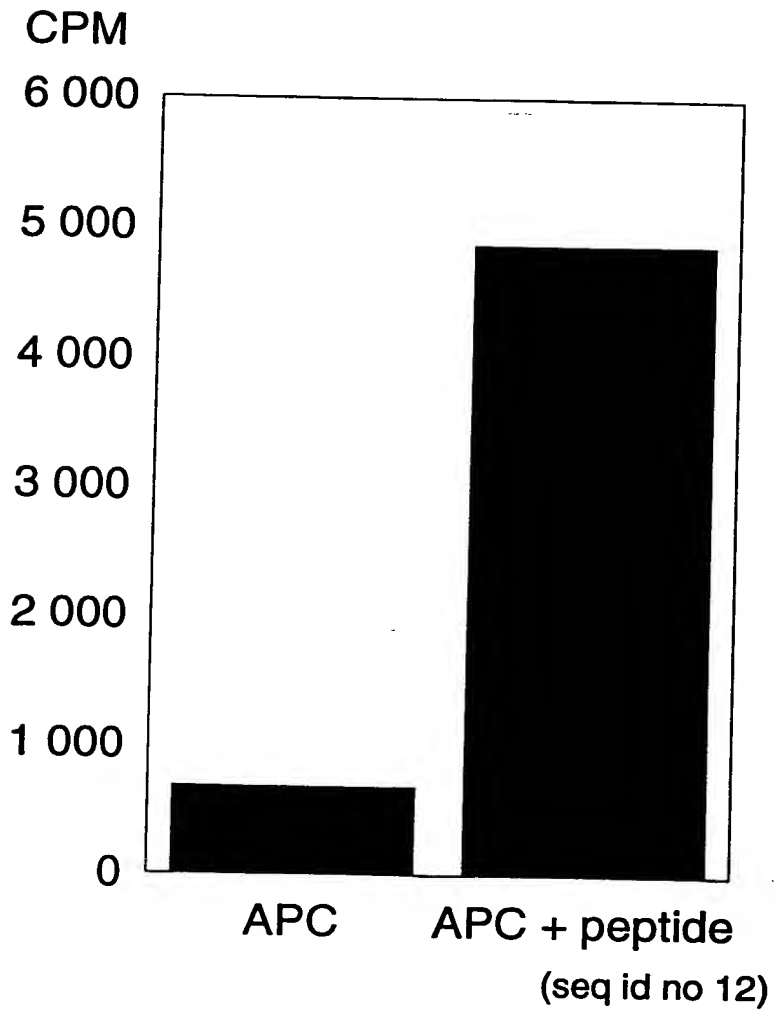
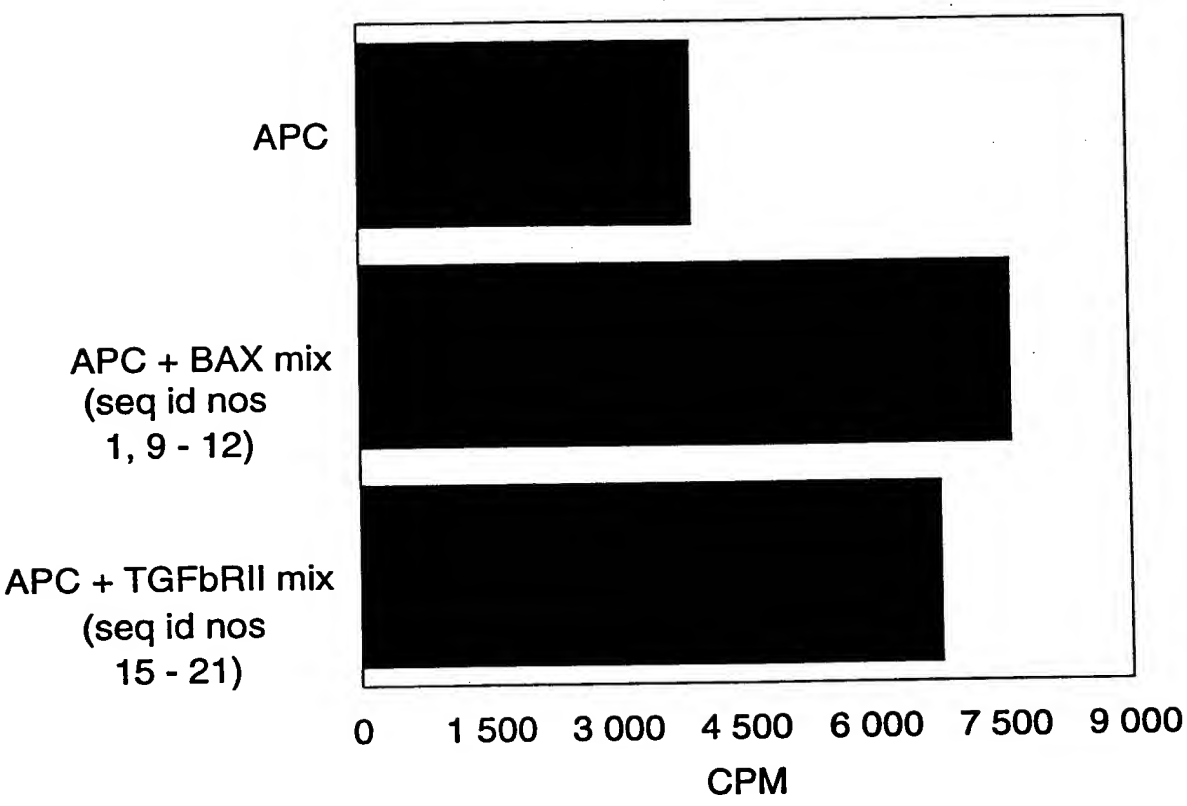


Fig. 2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(seq id nos
1, 9 - 12)
APC + TGFbRII mix
(seq id nos
15 - 21)
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3 000
4 500
6 000
7 500
9 000
CPM

Fig. 3

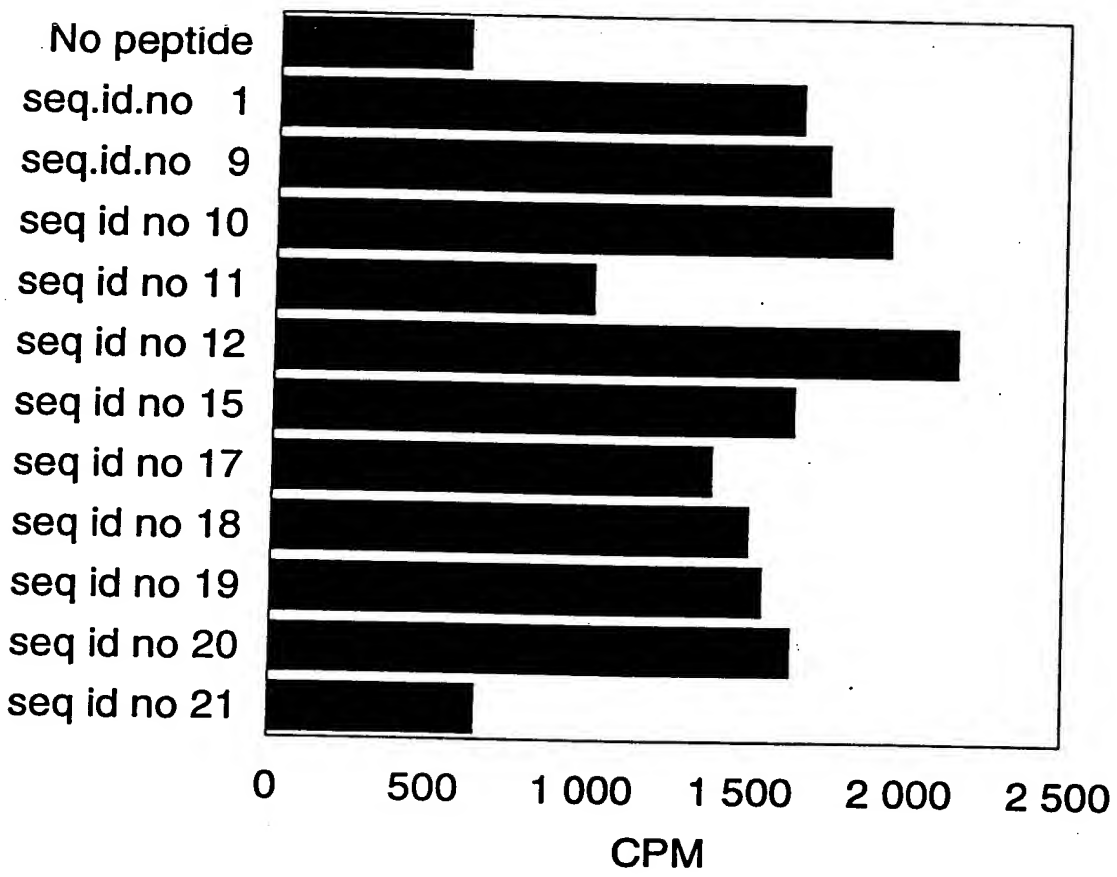
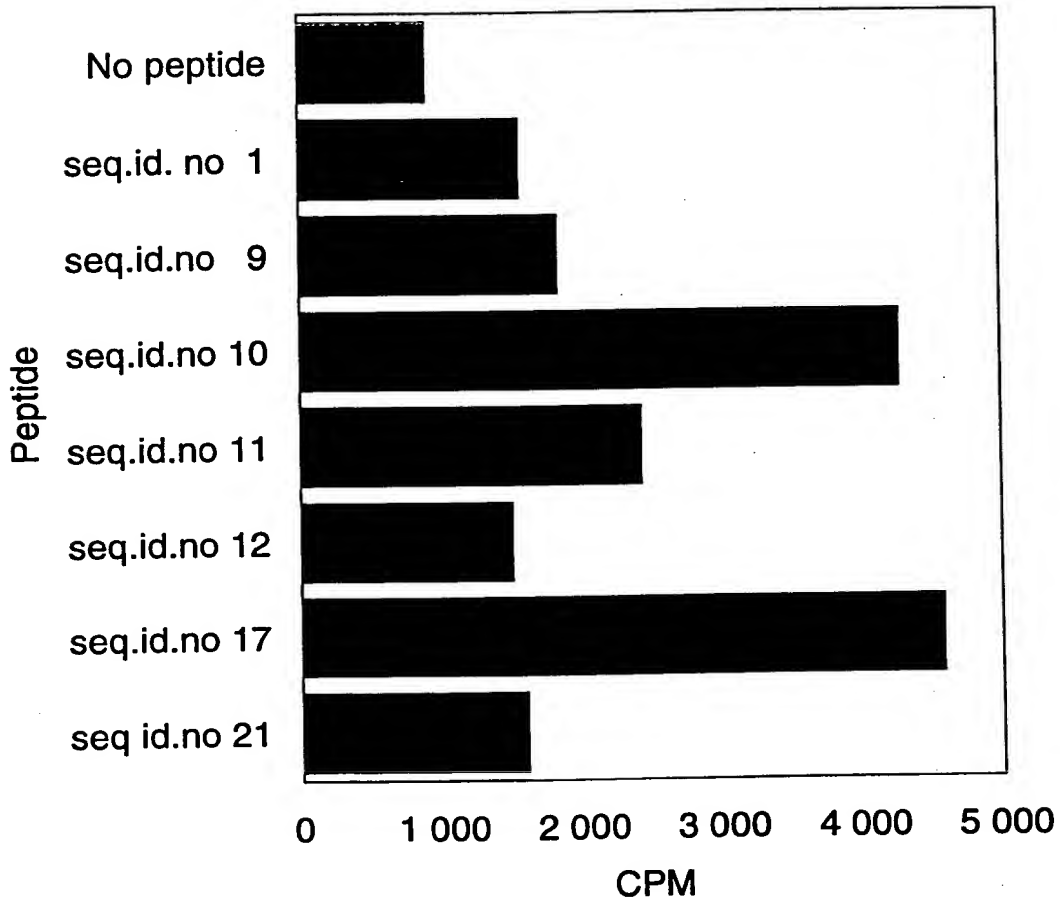


Fig. 4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2 000
3 000
4 000
5 000
CPM

Fig. 5

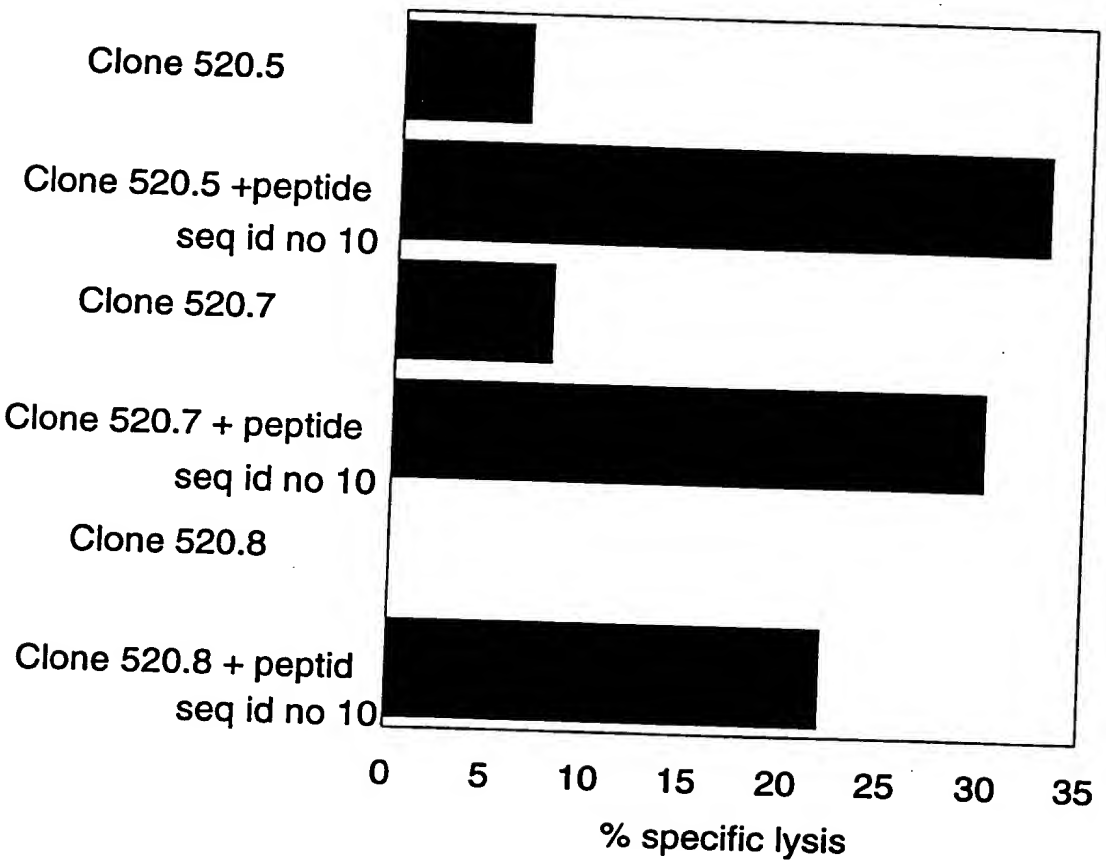
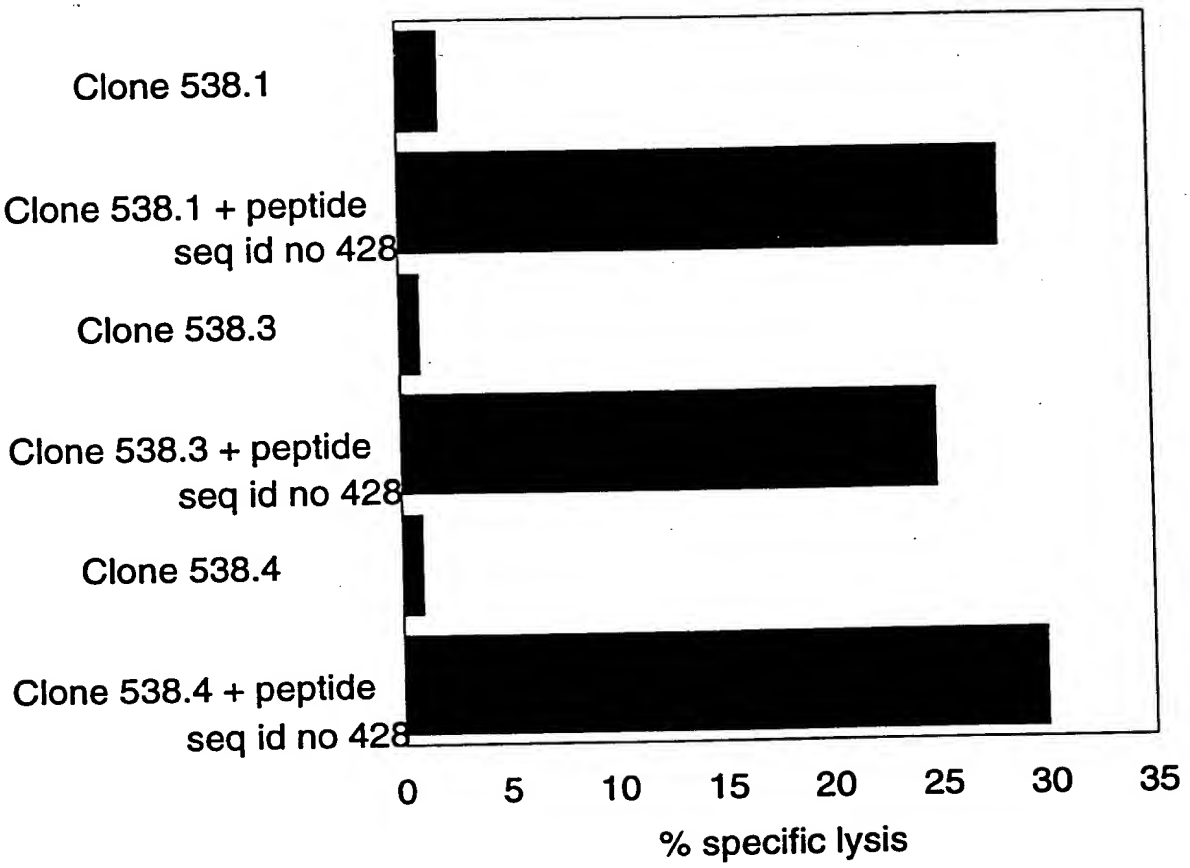


Fig. 6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35
% specific lysis

Fig. 7